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Changing Management of Acute Ischaemic Stroke: the New Treatments and Emerging Role of Endovascular Therapy

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Opinion statement

Urgent reperfusion of the ischaemic brain is the aim of stroke treatment, and the last two decades have seen a rapid advancement in the medical and endovascular treatment of acute ischaemic stroke. Intravenous tissue plasminogen activator (tPA) was first introduced as a safe and effective thrombolytic agent followed by the introduction of newer thrombolytic agents as well as anticoagulant and antiplatelet agents, proposed as potentially safer drugs with more favourable interaction profiles. In addition to chemo-thrombolysis, other techniques including transcranial sonothrombolysis and microbubble cavitation have been introduced which are showing promising results, but await large-scale clinical trials. These developments in medical therapies which are undoubtedly of great importance due to their potential widespread and immediate availability are paralleled with gradual but steady improvements in endovascular recanalisation techniques which were initiated by the introduction of the MERCI (Mechanical Embolus Removal in Cerebral Ischemia) and Penumbra systems. The introduction of the Solitaire device was a

significant achievement in reliable and safe endovascular recanalisation and was followed by further innovative stent retrievers. Initial trials failed to show a solid benefit in endovascular intervention compared with IV-tPA alone. These counterintuitive results did not last long, however, when a series of very well-designed randomised controlled trials, pioneered by MR-CLEAN, EXTEND-IA and ESCAPE, emerged, confirming the well-believed daily anecdotal evidence. There have now been seven positive trials of endovascular treatment for acute ischaemic stroke. Now that level I evidence regarding the superiority of endovascular recanalisation is abundantly available, the clinical challenge is how to select patients suitable for intervention and to familiarise and educate stroke care providers with this recent development in stroke care. It is important for the interventional services to be provided only in comprehensive stroke centres and endovascular interventions attempted by experienced well-trained operators, at this stage as an adjunct to the established medical treatment of IV-tPA, if there are no contraindications.

Introduction

Stroke is considered one of the major public health problems and the third most costly health condition in developed countries [1]. It is the most common cause of adult disability in these countries, requiring long-term costly rehabilitation, and is the principal cause of 1 out of every 16 deaths [2]. The majority of the strokes are ischaemic in nature with only about 15 % being due to haemorrhagic events [2].

In ischaemic stroke, a core area of tissue dies due to under-perfusion and an area of hypo-perfused tissue with patent collateral vessels remains salvageable. This has been referred to as the "penumbra" which, if revascularised in a timely manner, could be saved [3]. Therefore, urgent recanalisation of the occluded artery and restoration of blood flow are considered the most important therapeutic step to reperfuse the threatened brain parenchyma before an irreversible infarction is established, in order to reduce morbidity and mortality [4]. Studies have estimated 1.8 days of added healthy life benefit for each minute reduction in time to treatment [5], and a meta-analysis has demonstrated that successful recanalisation increases the chance of a good functional outcome with an odds ratio of 4.43 (95 % CI 3.32–5.91) and reduced mortality at 3 months (OR 0.24, 95 % CI 0.16–0.35) [6].

Almost 20 years ago, in 1996, intravenous tissue plasminogen activator (IV-tPA) was approved as the first thrombolysis medication and practically the only treatment option in ischaemic strokes, when administered within 3 h from onset. However, its success rate in recanalisation is reduced in large vessel occlusion and was never shown to be more than 50 % and is more likely to be around 30 % [1, 7]. This partial success in recanalisation, with critical time limitations, makes tPA less than ideal in managing a large proportion of the stroke patients with large vessel occlusion. In fact, it has been shown that approximately 70 % of patients with acute ischaemic stroke are not eligible for thrombolysis, mainly due to delayed presentation [8, 9].

Overall, the success of intravenous thrombolysis depends on numerous factors including thrombus type, location and extent, collateral circulation, underlying comorbidities, patient's age, time to commencement of treatment and time to recanalisation [2]. Furthermore, studies have shown that large calibre proximal arteries are unlikely to be responsive to chemical thrombolysis alone [7, 10, 11]. Clinical trials have also shown that the likelihood of recanalisation negatively correlates with thrombus burden, with those having a clot size more than 8 mm in length having a significantly lower chance of achieving recanalisation by IV-tPA alone [2, 12].

The effectiveness of IV-tPA is also affected by the composition of the occlusive clot with emboli originated from large vessel atherosclerotic lesions shown to be less responsive, compared with the usually recanalisable fibrin-rich cardioembolic thrombi [13]. In addition, early reocclusion of the arteries has been shown in up to 20 % of cases, when recanalised initially by IV-tPA [14].

Therefore, there have been major initiatives over the last several years to examine and develop new techniques to improve recanalisation rates and clinical outcome. These newly proposed therapeutic techniques consist not only of other extra-arterial methods of thrombolysis but also a variety of endovascular techniques with the aim of improving revascularisation rates and clinical outcome.

Extra-arterial thrombolysis

Intravenous tPA is the standard first-line treatment in those who are eligible which normally follows a noncontrast CT brain excluding a haemorrhagic stroke. Provided no contraindications exist, it is administrated at a dose of 0.9 mg/kg (maximum of 90 mg), with 10 % of the medication given as a bolus and the remainder infused over 1 h [2, 15, 16]. The safety and efficacy of IV-tPA within the first 3 h of the onset of the symptoms was demonstrated in the National Institute of Neurological Disorders and Stroke (NINDS) study [17]; however, the envelope of the time limitation was stretched in subsequent research studies, like ECASS 3 (European Cooperative Acute Stroke Study 3) [18], with the proposed guidelines changed accordingly to include those patients who presented within 4.5 h [1, 15, 19]. Subgroup analyses of the data from the IST-3 trial and SITS-IST (Ischemic Stroke Recorded in the Safe Implementation) study furthermore showed no statistically significant detrimental effect for tPA treatment in those who presented up to 6 h after onset compared with 4.5 or 3 h, suggesting that delayed intravenous (IV) thrombolysis can still have beneficial effects [9, 20, 21].

Sonothrombolysis aims to increase the efficacy of IV-tPA by using the effect of energy delivered by sound waves on fibrin strands in the thrombus. Its feasibility and safety have already been proven by the CLOTBUST (Combined Lysis of Thrombus in Brain Ischemia With Transcranial Ultrasound and Systemic TPA) study [10, 22–24]. However, its efficacy is being further investigated in the phase III CLOTBUST-ER (Randomized, Placebo-Controlled, Double-Blind Study of the Combined Lysis of Thrombus With Ultrasound and Systemic Tissue Plasminogen Activator for Emergent Revascularization) study with recruitment completed but the results are yet to be released [25]. A similar idea has been proposed by using ultrasound microbubble contrast agents, which lead to cavitation within the occlusive thrombi, helping their degradation in the presence of IV-tPA, which is being examined in the TUSCAN (Transcranial Ultrasound in Clinical Sonothrombolysis) study [1, 8, 10, 26, 27, 28•].

On the other hand, there is a definite lack of evidence for the benefit of combination therapies of IV-tPA with anticoagulation or antiplatelet agents. The recent ARTIS (Antiplatelet Therapy in Combination with recombinant tPA Thrombolysis in Ischemic Stroke) study demonstrated an increased risk of symptomatic intracranial haemorrhage with concurrent administration of aspirin [10, 19, 29, 30].

Parallel to the worldwide ongoing use of tPA as the only clinically approved thrombolytic agent in ischaemic stroke (which works by converting plasminogen into active plasmin [2, 18, 31•, 32]), there are ongoing attempts to investigate other potential agents with the hope of finding substitutes with better risk-benefit profile, particularly given the emerging evidence of a potential detrimental effect of tPA on the blood-brain barrier and its resultant neurotoxicity [2, 10, 33–35].

Tenecteplase was one of the first agents introduced as a semi-synthetic and potential substitute for tPA, which has a longer half-life and an increased affinity to fibrin [10, 30, 36, 37], with at least one study so far demonstrating increased recanalisation success rate compared with IV-tPA with good final

clinical outcome and no statistically significant difference in the risk of haemorrhagic complications [37]. However, NOR-TEST (Norwegian Tenecteplase Stroke Trial) is an ongoing RCT on tenecteplase with the results yet to be released [38].

Desmoteplase also demonstrates a higher affinity for fibrin with longer half-life compared with tPA. It is found in the bat saliva and has been suggested as an alternative thrombolytic agent. However, increased symptomatic haemorrhage was demonstrated in the initial feasibility and safety phase of the DIAS (Desmoteplase In Acute Ischemic Stroke) study, requiring dosage modification in the following phase II DEDAS (Dose Escalation of Desmoteplase for Acute Ischemic Stroke) and phase III DIAS-2 studies [10, 39]. Although there were unfavourable results released from the DIAS-2 study, however, given the subsequent criticisms regarding its sample size and patient selection, desmoteplase was again the subject of investigation in the phase III DIAS-4 study with preliminary results confirming its inferiority with the final results to be published in the near future [10, 40–42].

In addition to the above-mentioned novel thrombolytic agents, there are ongoing research studies into the potential benefit of the new anticoagulation and antiplatelet agents.

Ancrod is an anticoagulant agent extracted from the viper's venom which reduces fibrinogen levels and blood viscosity. Although an initially better immediate outcome was demonstrated in STAT (Stroke Treatment with Ancrod Trial) in those patients with acute ischaemic stroke who received ancrod infusion, it was associated with a marginally significant increase in the risk of symptomatic haemorrhage with the long-term benefit being questionable [10, 43–45].

Argatroban, on the other hand, is a direct thrombin inhibitor which was shown to be of no significant benefit in the treatment of patients with acute ischaemic stroke who presented late, in the phase I ARGIS (Argatroban Anticoagulation in Patients with Acute Ischemic Stroke) study. However, it demonstrated a statistically significant benefit when combined with conventional tPA infusion in the ARTTS (Argatroban Tissue-Type-PA Stroke) study, increasing the recanalisation rate [10, 23, 46–51], and is now into the second phase of clinical investigation [52]. Other agents from this family include *hirudin*, *bivalirudin*, *desirudin*, *lepirudin*, *dabigatran*, *melagatran* and *ximelagatran*, and their roles in the management of acute ischaemic stroke are yet to be fully investigated [53–55].

Relatively novel GP-IIb/IIa antiplatelet agents, as direct platelet activation inhibitors [56], were also tried as adjuvant treatments in the setting of coronary artery occlusion, with immediate recanalisation improvement, but with questionable long-term benefit in that context [10, 57, 58], and now are the subject of multiple clinical trials to study their potential benefit in the management of ischaemic stroke.

Tirofiban was initially suggested for those patients with acute ischaemic stroke with delayed presentation and has been shown not only to be safe but also with a marginal benefit in decreasing mortality in the long term in the phase II SaTIS (Safety of Tirofiban in Acute Ischemic Stroke) trial [9, 10, 24].

Abciximab, however, demonstrated a significantly higher rate of symptomatic intracranial haemorrhage in the phase II AbESTT (Abciximab in Emergency Treatment of Stroke Trial) RCT compared with the control group with no

significant benefit in outcome [9, 10, 59, 60].

Eptifibatide, on the other hand, decreased the risk of symptomatic intracranial haemorrhage when combined with IV-tPA compared with those treated with IV-tPA alone in the phase II CLEAR-ER (Combined Approach to Lysis Utilizing Eptifibatide and Recombinant Tissue Plasminogen Activator in Acute Ischemic Stroke) study, with a trend towards a better final clinical outcome [61].

Other members of this antiplatelet aggregation family, e.g. *roxifiban* and *orbofiban*, have also been the subject of different phases of clinical trials, with their advantage over conventional treatments yet to be shown [62, 63].

Endovascular treatment

PROACT II (Prolyse in Acute Cerebral Thromboembolism) was the first study to examine the efficacy of intra-arterial thrombolysis instead of intravenous thrombolysis. Despite the fact that some of the usual resilient patterns of occlusion such as ICA thrombosis were excluded from the study, there were still relatively poor recanalisation rates in patients treated with IA urokinase, with questionable overall clinical benefit, which could even be partially related to the heparin [32, 64]. Although the following IMS II (Interventional Management of Stroke II) trial demonstrated a slightly better outcome in those patients treated with intra-arterial tPA infusion via an EKOS (EkoSonic Endovascular System) microcatheter, there was also a higher rate of symptomatic intracranial haemorrhage demonstrated in this group with an overall poor recanalisation rate [65], demonstrating a failure in providing a tangible advantage in this technique [66].

Mechanical thrombectomy has always had the appealing potential of rapid recanalisation and accelerated reperfusion with a potential for reduced haemorrhagic risk [1]. The MERCI (Mechanical Embolus Removal in Cerebral Ischemia) device was a corkscrew-shaped device with helical nitinol loops, which was specifically designed for placement into the thrombus for enbloc removal. It was the first officially approved thrombectomy device with its safety and feasibility assessed in MERCI and multi-MERCI trials [28•, 67–69]. The device was practically only useful for proximal large arterial occlusions, predominantly M1, and although this was associated with an increased recanalisation rate in particular when combined with IV-tPA, approaching 70 %, there was no overall clinical benefit shown in the final outcome of patients with an increase in mortality rate noted in those treated with this device [2, 67, 70].

The earliest iteration of the PT-PAD (Penumbra Thrombus Perturbation and Aspiration Device) was a clot aspiration catheter with an inner mechanical clot separator, which was shown to be safe in the PPS (Penumbra Pivotal Stroke) trial [71]. Despite its relatively high recanalisation rate of ~80 %, the trial failed to show any significant benefit in the final clinical outcome [68]. However, the newer Penumbra system is much simpler, but with more advanced catheter technology, comprised of Max/Neuron family distal intracranial catheters for aspiration thrombectomy using a controlled vacuum pump system, which are the subject of an ongoing trial, THERAPY (Table 1). THERAPY is a trial to assess the safety and effectiveness of the new Penumbra system as an adjunctive treatment to IV-tPA, over IV-tPA alone (an example of suction thrombectomy

Table 1. Recent randomised controlled trials of endovascular stroke therapy (adopted and modified from previously published articles as referenced [87••, 91••, 92••, 93, 95, 96, 118])

Trial	MR-CLEAN	ESCAPE	EXTEND-IA	SWIFT-PRIME	REVASCAT	THERAPY	THRACE[a]
Important inclusion criteria	NIHSS ≥2 Age ≥18 Anterior circulation large artery occlusion[b]	NIHSS >5 ASPECTS >5 Moderate/good collaterals[b]	Eligible for IV-tPA (<4.5 h) Age 18–80 Ischaemic core <70 cm^3 Mismatch[c]	Eligible for IV-tPA (<6 h) Age 18–85 NIHSS 8–29 ASPECTS ≥6	Age 18–80[d] NIHSS ≥6 ASPECTS ≥7[d]	Eligible for IV-tPA (<4.5 h) Age 18–85 NIHSS ≥8 Clot length ≥8 mm[e]	Eligible for IV-tPA (<4.5 h) Age 18–80 NIHSS 10–25
Interventional arm (I)	Intra-arterial therapy	Intra-arterial therapy	Solitaire-FR stent retriever	Solitaire-FR stent retriever	Solitaire-FR stent retriever	Penumbra aspiration system	Endovascular thrombectomy
Control arm (C)	Best medical management[f]	Best medical management[f]	IV-tPA only	IV-tPA only	Best medical management[f]	IV-tPA only	IV-tPA only
Time to intervene[g] (h)	<6	<12	<4.5	<6	<8	<4.5	<5
Number of patients, T (I, C)	500 (*I* = 233, *C* = 267)	315 (*I* = 165, *C* = 150)	70 (*I* = 35, *C* = 35)	196 (*I* = 98, *C* = 98)	206 (*I* = 103, *C* = 103)	108 (*I* = 54, *C* = 54)	385 (*I* = 190, *C* = 195)
Mean age	*I* = 65.8, *C* = 65.7	*I* = 71, *C* = 70	*I* = 68.6, *C* = 70.2	*I* = 66.3, *C* = 65.0	*I* = 65.7, *C* = 67.2	Not reported	*I* = 62, *C* = 62
Median NIHSS	*I* = 17, *C* = 18	*I* = 16, *C* = 17	*I* = 17, *C* = 13	*I* = 17, *C* = 17	*I* = 17, *C* = 17	Not reported	*I* = 17, *C* = 17
Median ASPECTS	*I* = 9, *C* = 9	*I* = 9, *C* = 9	Not assessed	*I* = 9, *C* = 9	*I* = 7, *C* = 8	Not reported	Not reported
Received IV-tPA	*I* = 87.1 %, *C* = 90.6 %	*I* = 72.7 %, *C* = 78.7 %	*I* = 100 %, *C* = 100 %	*I* = 100 %, *C* = 100 %	*I* = 68.0 %, *C* = 77.7 %	*I* = 100 %, *C* = 100 %	I = 100 %, *C* = 100 %
Median time to groin puncture (min)	260	241[h]	210	224	269	226	255[h]
Stent retriever (%)	81.5	86.1	100	100	100	Only aspiration	Not reported
Increased mRS 0–2 at 90 days	13.5 %* (*I* = 32.6, *C* = 19.1 %)	23.7 %* (*I* = 53.0 %, *C* = 29.3 %)	31.4 %* (*I* = 71.4 %, *C* = 40.0 %)	24.7 %* (*I* = 60.2 %, *C* = 35.5 %)	15.5 %* (*I* = 43.7 %, *C* = 28.2 %)	7.6 % (*I* = 38.0 %, *C* = 30.4 %)	12.1 %* (I = 54.2 %, *C* = 42.1 %)
Decrease in mortality at 90 days	1.1 % (*I* = 21.0 %, *C* = 22.1 %)	8.6* (*I* = 10.4 %, *C* = 19.0 %)	11.4 % (*I* = 8.6 %, *C* = 20.0 %)	3.2 % (*I* = 9.2 %, *C* = 12.4 %)	−2.9 % (*I* = 18.4 %, *C* = 15.5 %)	11.9 % (*I* = 12.0 %, *C* = 23.9 %)	0.6 % (I = 12.5 %, *C* = 13.1 %)
TICI grade 2b/3 recanalisation (%)	58.70	72.40	86.20	88.00	65.70	Not reported	Not reported
Symptomatic ICH	*I* = 7.7 %, *C* = 6.4 %	*I* = 3.6 %, *C* = 2.7 %	*I* = 0 %, *C* = 5.7 %	*I* = 0 %, *C* = 3.1 %	*I* = 1.9 %, *C* = 1.9 %	*I* = 10.9 %, *C* = 11.3 %	NOT REPORTED

REVASCAT Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours, *SWIFT-PRIME* Solitaire FR as Primary Treatment for Acute Ischemic Stroke, *THERAPY* Assess the Penumbra System in the Treatment of Acute Stroke, *THRACE* Trial and Cost Effectiveness Evaluation of Intra-Arterial Thrombectomy in Acute Ischemic Stroke

*$P < 0.05$, statistically significant

[a]Preliminary results from 2015 European Stroke Organization Conference (Glasgow, UK)

[b]Assessed on CTA

[c]Mismatch defined, based on CT perfusion imaging, as a match ratio of >1.2 and an absolute mismatch volume of >10 cm [3]

[d]After enrolment of 160 patients, the inclusion criteria were modified to include patients with age 81–85 who had an ASPECTS >9

[e]Assessed on CT/CTA

[f]Including IV-tPA if no contraindication

[g]Time window eligible for intervention from the onset of symptoms

[h]Time from stroke onset to first reperfusion (time to groin puncture not reported)

depicted in Fig. 1). The preliminary results of this study have been quite encouraging with a 7.6 % increase in good outcome as per modified Rankin Scale (mRS), 11.9 % decrease in mortality at 90 days and no difference in complication rate.

The idea of using stents in the treatment of acute ischaemic stroke followed from the introduction of intracranial self-expanding stents for the treatment of intracranial atherosclerotic stenosis. The initial attempts made in the treatment of acute ischaemic stroke were by deployment of the stent across the thrombus at the occluded segment [2, 66, 72, 73]. One of the major conceivable complicating factors of this therapy was the need for concurrent antiplatelet-anticoagulation therapy and potential risk of haemorrhage [2, 74]. Despite the good technical success and significant improvement in the 90-day clinical outcome, the SARIS (Stent-Assisted Recanalization Acute Ischemic Stroke) study demonstrated significant subsequent in-stent stenosis requiring aggressive medical management with a resultant increased rate of haemorrhagic transformation [75, 76].

On the other hand, the introduction of detachable stents for stent-assisted coiling of cerebral aneurysms raised the possibility of using stents, which would retrieve a clot in mechanical intracranial thrombectomy, with the further advantage of rapid recanalisation without the above-mentioned risks and complications of a permanent stent. The first two devices to be approved for this purpose were Solitaire-FR™ from Covidien® and Trevo™ from Stryker®, which were followed by similar products including Trevo-ProVue™ (Stryker®), Revive™ (Johnson & Johnson®), EmboTrap™ (Neuravi®), Eric™ (MicroVention®), Catch™ and Catch-Mini™ (Balt®). Contrary to the suction thrombectomy or even stent insertion [77], these devices not only displace the thrombus to the periphery of the vessel and temporarily restore the flow, they also capture the thrombus by incorporating the clot through their interstices to make it possible to withdraw the trapped clot when the stent is removed [66, 78].

However, the initial promise demonstrated by the SWIFT (SOLITAIRE With the Intention For Thrombectomy) trial showing the superiority of the Solitaire stent over the MERCI retriever, with overall recanalisation rate of ~90 % [79], further empowered by the phase II TREVO-2 (Thrombectomy Revascularisation of Large Vessel Occlusions in Acute Ischaemic Stroke) trial [80], suddenly diminished when three subsequent major RCTs failed to demonstrate any significant benefit in the final clinical outcome in endovascular intervention [66].

IMS III (Interventional Management of Stroke III) was a randomised control study, prematurely halted two thirds through its recruitment, when significant inferiority was noted in the endovascular intervention arm [81], which in retrospect may have been due to multiple inherent flaws in the study design, e.g. heterogeneity of the sample groups, and the interventional methods, and finally under-representation of the new stent retriever devices, which were only used in a small number of cases, despite their clear technical superiority [1, 7, 12, 64, 80, 82]. Despite the fact that SYNTHESIS (Synthesis Expansion: A Randomized Controlled Trial on Intra-arterial Versus Intravenous Thrombolysis in Acute Ischaemic Stroke), another unsuccessful study, benefited from a relatively better RCT design, it most certainly still suffered from multiple major flaws including the absence of a strict policy for vascular imaging to identify those with large arterial occlusion prior to intervention [64, 83]. Although the

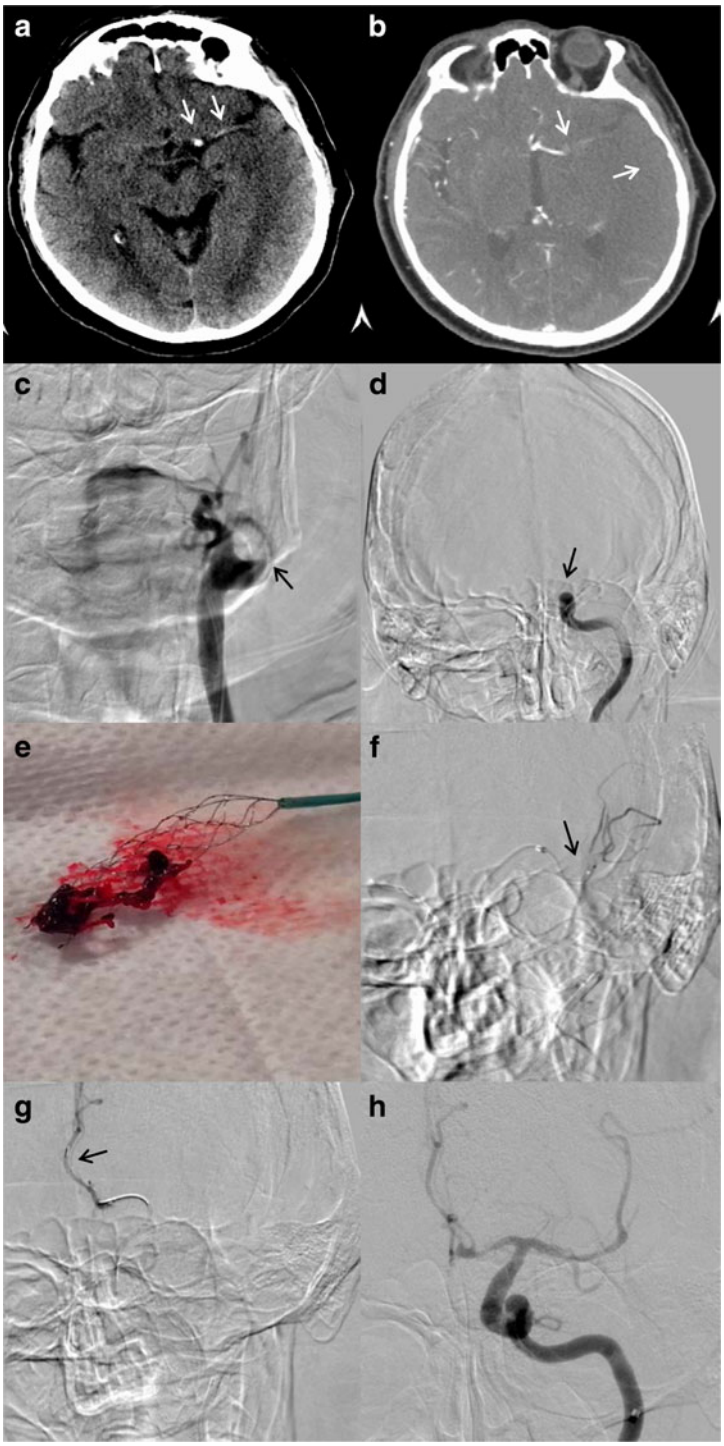

Fig. 1. A case of difficult thrombectomy, utilising different techniques. **a** Hyperdense left MCA sign, with extension into the ipsilateral carotid terminus. **b** Occluded left carotid terminus and MCA on CTA with severe paucity of collaterals. **c** ICA occlusion from the bulb. **d** ICA recanalisation with carotid-T occlusion on angio with no MCA or ACA flow. **e** Partial flow restoration by Solitaire stent retriever thrombectomy. **f** Aspiration thrombectomy to improve MCA bifurcation flow. **g** ACA Catch-Mini stent retriever recanalisation. **h** TICI-2b final angio run. On each image *arrows* indicate the exact location of the point described by the relavant caption.

MR-RESCUE (Mechanical Retrieval and Recanalisation of Stroke Clots Using Embolectomy) trial tried to exploit advantages of advanced imaging techniques to stratify patients for the trial in multiple different arms, it still suffered from poor statistical power due to under-sampling in each group as well as a liberal intervention time window and poor overall technical success and recanalisation rates [3, 64, 84, 85].

The above-mentioned undoubtedly counterintuitive results certainly hindered activities regarding endovascular intervention in acute ischaemic stroke around the world until, in the second half of 2014, the Dutch MR-CLEAN (Multicenter Randomized CLinical trial of Endovascular treatment for Acute ischaemic stroke in the Netherlands) study demonstrated superiority in endovascular intervention, when the trial results were presented at the 9th World Stroke Congress (Table 1) [66].

MR-CLEAN was a randomised controlled trial which recruited 500 patients older than 18 years of age, with National Institutes of Health Stroke Scale (NIHSS) of at least 2 and anterior circulation large artery occlusion confirmed on CT angiography (CTA), presenting no later than 6 h from the onset of symptoms. All patients received full standard medical management, including IV-tPA where possible, and were randomised into an intra-arterial interventional group (233 patients) and control with ~82 % of interventional patients treated by stent retrievers. The median NIHSS was 17 in the intervention and 18 in the control group, with the median Alberta Stroke Program Early CT Score (ASPECTS) of 9 for both, and 87.1 % and 90.6 % received IV-tPA in each group, respectively. Approximately 80 % of the patients who were intervened were completely recanalised in 24 h, with an odds ratio of 6.9 (95 % CI 4.3–10.9) compared to the control arm. This was associated with a significantly smaller infarct volume at 1 week in the interventional group compared with the control, 49 versus 80 ml, leading to a much better clinical outcome at 3 months (mRS less than 2, 33 versus 19 %) (Table 1) [86, 87••].

The positive and promising results from MR-CLEAN rejuvenated optimism regarding an endovascular treatment of stroke which was further confirmed by the EXTEND-IA (Extending the Time for Thrombolysis in Emergency Neurological Deficits-Intra-Arterial) and ESCAPE (Endovascular Treatment for Small Core and Proximal Occlusion Ischaemic Stroke) results which were very notably positive. These two studies were halted by respective data safety and monitoring boards as equipoise was no longer in place after MR-CLEAN. The results of both were presented and published in February 2015.

EXTEND-IA was an Australian and New Zealand multicentre randomised controlled trial of intra-arterial reperfusion therapy after standard dose of IV-tPA versus IV-tPA alone. Patients were carefully selected cases with both large anterior circulation arterial occlusion and small core infarct using CT perfusion, analysed/processed by RAPID (Rapid Processing of Perfusion and Diffusion) [88], a technique that was developed at Stanford University with NINDS funding [89, 90]. Patients were included if they presented no later than 4.5 h after onset of symptoms, with the estimated infarct core less than 70 ml, or if there was a mismatch ratio greater than 1.2 between the estimated core and the under-perfused parenchyma. Patients were randomised into IV-tPA with subsequent Solitaire stent retrieval and IV-tPA alone [91••]. When the study was terminated, 70 patients had been enrolled with 35 in each arm. Median NIHSS was 17 and 13 in the interventional and control groups, respectively, with

median age of 68.6 and 70.2 years. Recanalisation rate was more than 86 % in the interventional group with no significant difference in symptomatic intracranial haemorrhage. Significant improvement in the outcome was demonstrated in the interventional group with 31.4 % increase in those with mRS ≤2 and decreased mortality of 11.4 % compared to the control group (Table 1).

ESCAPE was a Canadian study with enrolment centres across Europe and North America, recruiting patients with NIHSS and ASPECTS of more than 5 with estimated moderate-to-good collaterals on multiphase CTA who did not present later than 12 h post onset of symptoms [92••]. At the time the study was terminated, 315 patients were enrolled with 165 and 150 allocated to the interventional and control arms, respectively, with median age and NIHSS of 71/70 and 16/17, respectively. The median ASPECTS was 9 in both arms with just below 80 % of the patients receiving IV-tPA. There was a significant increase in the overall favourable clinical outcome in those who underwent thrombectomy with a statistically significant decrease in mortality on a background recanalisation rate of approximately 70 % in the intervention arm (Table 1).

REVASCAT (Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours) [93] was a Spanish study which was again halted because of the broken equipoise. REVASCAT enrolled the first 160 patients aged between 18 and 80 who presented not later than 8 h post onset of symptoms with NIHSS equal to or more than 8 and ASPECTS of more than 6; however, the age criterion was subsequently modified to also include those aged between 81 and 85 if their ASPECTS was better than 9 [94]. In addition, a large anterior circulation artery occlusion was required to be demonstrated on CTA. Patients who received IV-tPA but failed to improve were included in the trial [94].

REVASCAT was terminated after 206 patients were randomised out of the initial target of 690 with 103 patients recruited in each arm. The average age of the subjects was 66.5 years with median ASPECTS of 7 and 8 for interventional and control groups, with 68 and 77 % of interventional and control arms receiving IV-tPA, respectively. The median NIHSS was 17 for both groups with all of the endovascular interventions performed using stent retrievers; however, the overall recanalisation rate was relatively lower (~65 %), in particular, when compared to the other trials, but no increase in the complication rate compared to the control arm. Although there was a significant increase in the number of patients with good outcome with an adjusted odds ratio of 2.1 (95 % CI 1.1–4.0) and the number needed to treat to cause a favourable outcome of 6.4, there was a slight increase in total mortality in the interventional group compared with the control, which was not statistically significant. This was a well-organised trial with only a handful of the stroke patients presenting to the participating institutes not randomised. However, a post IV-tPA neurovascular imaging requirement as a part of the study protocol inevitably increased the delay to intervention and could together with increased times to enrol those who fail IV therapy be a contributing factor to the above-mentioned higher mortality [93].

SWIFT-PRIME (Solitaire™ FR as Primary Treatment for Acute Ischemic Stroke) trial also started with a design very similar to EXTEND-IA with a great emphasis on perfusion assessment of the infarcted core, which was again halted after demonstrating overwhelming efficacy for the endovascular group after the

Table 2. Randomised controlled trials yet to be finished, concluded or published (adopted and modified from previously published articles as referenced [66, 95])

Clinical trial	Country	Total planned sample size	First patient in	No. of enrolled IV-tPA subjects	Status
BASICS	EU	750	April 2011	47	Enrolling
DAWN	USA and EU	500	February 2013	Not applicable	Enrolling
PISTE	UK and Norway	450	April 2013	59	Enrolling
POSITIVE	US	750	September 2013	Not applicable	Halted for <8 h but enrolling for 8–12 h
RESILIENT	Brazil	690	March 2015	0	Recently started
THRILL	Germany and Austria	600	May 2014	Not applicable	Halted by DSMC

BASICS Basilar Artery International Cooperation Study, *DAWN* Trevo and Medical Management vs. Medical Management Alone in Wake Up and Late Presenting Strokes, *PISTE* Pragmatic Ischaemic Stroke Thrombectomy Evaluation, *POSITIVE* Perfusion Imaging Selection of Ischemic Stroke Patients for Endovascular Therapy, *RESILIENT* Endovascular Treatment With Solitaire FR vs Best Medical Therapy in Acute Ischemic Stroke, *THRILL* Comparison of Thrombectomy and Standard Care for Ischemic Stroke in Patients Ineligibility for Tissue Plasminogen Activator Treatment

196th patient was enrolled out of the total of 833 initially planned [95]. From the technical point of view, however, it is important to note that given the lack of standardisation of perfusion data, the current role of perfusion imaging is more to "rule-in" late presenters on the basis of penumbra rather than to "rule-out" early presenters, and attainment of perfusion data also should not significantly delay potential treatments [66].

Interestingly, the final study of this group of six, the French phase III THRACE (Trial and Cost Effectiveness Evaluation of Intra-arterial Thrombectomy in Acute Ischemic Stroke), despite its relatively liberal approach to preprocedural imaging-based selection as well as endovascular techniques allowed into the study, was also terminated after positive intermediate analyses of the data from the first 395 enrolled patients. This may be significant as it may indicate overall endovascular superiority even in a less stringent patient selection routine, using a variety of techniques, although the final results are yet to be published [95, 96].

On the other hand, THRACE was the only trial in this wave of studies to include vertebrobasilar strokes. It is important to understand that although posterior circulation strokes only constitute less than 10 % of all large vessel ischaemic events, they appear to be a different entity all together with much poorer outcome with a few studies demonstrating significant mortality in the setting of unsuccessful recanalisation [2, 97, 98]. Prospective studies and in particular RCTs are hampered by relative low numbers and heterogeneity of acute vertebrobasilar occlusions. Nevertheless, BASICS (Basilar Artery International Cooperation Study), an observational registry of 592 patients, despite demonstrating a positive trend, failed to prove a statistically significant superiority of endovascular intervention over IV-tPA alone [99]. Further studies are emerging, claiming good recanalisation rates in vertebrobasilar occlusion with endovascular techniques, in particular using stent retrievers, with evidence

increasing for good outcome and decrease in mortality, but at this stage, the rationale for aggressive treatment in vertebrobasilar occlusion is principally based on anecdotal evidence [100].

There are further ongoing thrombectomy trials (Table 2), e.g. the Brazilian study of RESILIENT, the transpacific trial of DAWN, the British and Norwegian trial of PISTE and the American trial of POSITIVE, as well as those yet to be concluded and published, e.g. Central European study of THRILL, which will provide further evidence on the management and appropriate intervention in acute ischaemic stroke [95].

Further meta-analysis of the pooled data from these studies will be performed in order to have enough statistical power, making detailed subgroup analyses possible. Such an approach will avoid the need for larger randomised controlled trials and will help provide advice on the generalisability and universality of this technique, as well as optimising patient selection and generating realistic outcome expectations. Some work has already been done on attempting to predict outcome [101•, 102], but these have not reached widespread applicability [95, 103].

In addition to all of the above-discussed medical and endovascular treatments for acute ischaemic stroke to re-establish parenchymal perfusion, there is a relatively new category of research focused on potential neuroprotective strategies to minimise a detrimental effect of ischemia, prolonging the window of opportunity to intervene [104]. This include newly emerging chemical agents with anti-oxidative or anti-excitotoxicity effect, as well as those protecting the blood-brain barrier (BBB) or preventing neuronal apoptosis and autophagy [104], to physical modifications including induced hypothermia [105].

In fact, some of these treatments, e.g. nitric oxide [106] and cannabinoids, have had promising results in early animal models and ad hoc clinical investigations whilst awaiting further evidence. Meanwhile, although NeuMAST (Neuroprotection With Minocycline Therapy for Acute Stroke Recovery Trial) was terminated due to futility of the interim results [107], there is an ongoing effort to establish a trial for a newly developed agent, PSD-95 inhibitor (NA-1), with encouraging results from laboratory tests [108•].

Conclusions

Allowing for the overwhelming results of the recent trials, the main question is no longer whether combined chemo-thrombolysis and endovascular intervention is superior, but to identify those who will benefit from this approach and transferring them urgently to the endovascular stroke centre, with the main goal being reperfusion of the brain in a rapid and safe fashion as possible.

Implementation of a comprehensive service will be a great challenge as the treatment for ischaemic stroke is expected to have a major effect on public health. It is interesting to consider that the number of patients needed to treat (NNT) by percutaneous coronary intervention (PCI) in the setting of acute coronary syndrome (ACS) to prevent one death is approximately 20, whilst this number for acute ischaemic stroke, not only to avoid death but also to be functioning independently after 90 days of treatment, is only ~5 [109].

Now that the European Stroke Organisation has released an updated guideline recommending immediate availability of endovascular intervention to

patients with AIS due to large vessel occlusion within 6 h of onset, the major logistical challenge is how to provide such a service in a uniform and equal manner, to avoid extra time wasted in the referral chain whilst, on the other hand, also avoiding potential deskilling and under-experience of the operators in centres with insufficient procedural volumes [109].

One of the tempting proposals to tackle this challenge is to have mobile clinical and imaging diagnostic units accompanying the ambulance services, not only to exclude a haemorrhagic stroke and commence IV-tPA on the spot [110] but also to diagnose a large vessel occlusion and transfer the patient directly to a centralised endovascular centre for thrombectomy [111–113], an ambitious but certainly attractive idea, which is yet to be tested in practice.

There are now a growing number of national and international organisations proposing guidelines for the endovascular management of stoke, including the consensus statement released by ESO, ESMINT and ESNR [114], the management guideline published by the American Stroke Association [115], or the Canadian best practice recommendations [116], and individual institutions around the world can adopt or modify these and establish their own protocols based on their particular need and availability.

Final recommendations

1. Endovascular stroke intervention depends on the availability of skilled expertise in this technique; however, it should not preclude or delay initiation of the proven intravenous thrombolysis [2], if there are no contraindications.
2. Each emergency and radiology department should be equipped with preassembled kits of ready-to-use IV-tPA if indicated immediately after haemorrhage has been excluded with noncontrast CT brain. CTA should be performed immediately following noncontrast CT brain.
3. Endovascular intervention should only be performed in tertiary stroke centres of high volume with experienced multidisciplinary stroke teams and the required equipment and expertise available. The procedure should be conducted by interventional neuroradiologists with sufficient experience/training.
4. The infrastructure for rapid assessment, diagnosis and stabilisation of patients by a multidisciplinary team is required, or alternative transportation to a comprehensive stroke centre should be considered, where the specialist care and technology is available. Such a model has been previously proposed under the comprehensive stroke systems of care, which also requires the implementation of a set of guidelines and the establishment of a system for quality control and assessment [2, 117].
5. Stent retrievers should be the first-line treatment for endovascular treatment as they have shown the highest rates of recanalisation, although there is emerging evidence that fast and effective aspiration thrombectomy is also feasible and all available techniques should be utilised to achieve reperfusion as soon as possible.

6. Although there is now undeniable evidence for the effectiveness of endovascular intervention, the need for appropriate selection of candidates with imaging guidelines, in particular to confirm the presence of a large vessel occlusion and if possible a salvageable penumbra, should not be forgotten.
7. It is of paramount importance to minimise delays to treatment, by setting up a system of care consistent with existing regional structures to optimise the time of onset to the time of recanalisation, thus minimising brain tissue loss.

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Compliance with Ethical Standards

Conflict of Interest

Hamed Asadi declares no conflict of interest.

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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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