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Review Article

Endovascular stroke therapy

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ABSTRACT

Background: Following the development of intravenous thrombolysis as a successful treatment for ischaemic stroke, advances in neurointerventional radiology have facilitated endovascular approaches to treatment. This article reviews the available endovascular therapeutic options and their evidence-base.
Summary: Initial studies demonstrated that endovascular treatment of ischaemic stroke with intra-arterial thrombolysis and/or the use of clot-retrieval, thrombus aspiration and stent-retriever devices produced early recanalisation and reperfusion and improved neurological outcome. More recent randomised trials, however, have failed to show translation of recanalisation into successful clinical outcome with 'time to treatment' proving crucial. In this rapidly evolving field, combined therapy incorporating intravenous and intra-arterial thrombolysis in combination with endovascular clot-retrieval has been developed and further studies are expected to yield better evidence to guide the optimal treatment of acute cerebral ischaemia.

1. Introduction

Randomised controlled trials (RCTs) have shown ischaemic stroke to benefit from intravenous thrombolysis up to 3 and 4.5 h after symptom onset, with increasingly favourable outcomes the sooner the thrombolysis is administered [1–4]. This is in accordance with the phase "time is brain" and has been borne out by thrombolysis registry data [5,6]. It has been suggested that the benefit of intravenous thrombolysis may extend beyond 4.5 to 6 h in some patients but further studies are needed [7].

Favourable clinical outcome of intravenous thrombolysis has been associated with vessel recanalisation [8]. Studies have demonstrated reperfusion to be observed much less frequently in proximal large vessel artery occlusion compared with more distal vascular occlusion and recent studies have demonstrated recanalisation in only 18–25% of patients receiving intravenous thrombolysis for internal carotid artery (ICA), M1 middle cerebral artery (MCA) or basilar artery occlusion compared with 52% in M2 MCA occlusion [9–17]. Theoretically, administering thrombolytic agents directly into an area of clot or attempting to remove thrombus mechanically may increase efficacy. Endovascular intervention also has potential for faster recanalisation with a lower dose of lytic agent, visualisation of the clot being lysed (with prognostic implications), the possibility of increasing the time window from symptom onset to treatment and providing a therapeutic strategy for patients in whom intravenous thrombolysis is contraindicated [18]. In this article, we describe the endovascular therapeutic options developed and their evidence-base.

2. Methods

In March 2013, an electronic database search was performed of MEDLINE, EMBASE, HMIC, CINAHL and the Cochrane Library using the following MeSH and keywords: ischaemic; stroke; thrombolysis; intraarterial; endovascular; clot retrieval. All relevant articles between the years 1966 and 2013 were included. The resultant information was supplemented by extensive manual searching of references. Articles were evaluated against pre-defined criteria for eligibility and relevance that incorporated the following study characteristics: acute stroke patients, interventions, comparisons, outcomes and follow-up if pertinent. Inclusion of articles was based on an agreement between two independent reviewers (Ajay Bhalla, Jonathan Birns) using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement checklist [19].

2.1. Intra-arterial thrombolysis

Intra-arterial thrombolysis was developed as an alternative to intravenous therapy for acute ischaemic stroke, with positive results being demonstrated in preliminary investigations [20,21]. These initial observational studies were followed by seven RCTs that investigated the efficacy and safety of intra-arterial thrombolysis for acute ischaemic stroke (Table 1) [22–29]. Whilst the trials showed conflicting results, the majority of studies showed improvement in recanalisation and/or

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Table 1
Randomised controlled trials investigating the efficacy and safety of intra-arterial thrombolysis for acute ischaemic stroke.

Study	Subjects	Study design	Results	Conclusions
PROACT I [29]	n = 40 Acute MCA territory occlusion within 6 h of ictus NIHSS ≤ 30	Randomised 2:1 to receive 6 mg prourokinase plus heparin (n = 26) or heparin only (n = 14).	No significant difference in 90-day mRS ≤ 1 (31% vs 21%), mortality (27% vs 42%) or symptomatic ICH (15% vs 14%) between patients treated with prourokinase vs placebo. Recanalisation achieved in 57% patients treated with prourokinase vs 14% placebo patients (2p = 0.017). Both recanalisation and haemorrhage frequencies influenced by heparin dose.	Intra-arterial prourokinase was associated with superior recanalisation in acute ischaemic stroke compared with placebo. Heparin dose influenced haemorrhage frequency and recanalisation.
PROACT II [22]	n = 180 Acute MCA territory occlusion within 6 h of ictus NIHSS ≤ 30	Randomised to receive 9 mg of prourokinase plus heparin (n = 121) or heparin only (n = 59).	Significantly increased proportion of patients with 90 day mRS < 2 (40% vs 25%; p = 0.04), recanalisation (66% vs 18%; p < 0.001) and 24-hour symptomatic ICH (10% vs 2%; p = 0.06) in those treated with prourokinase vs placebo. No significant difference in mortality (25% vs 27%) between patients treated with prourokinase vs placebo.	Despite an increased frequency of early symptomatic ICH, intra-arterial prourokinase significantly improved clinical outcome at 90 days.
Ducrocq et al. [23]	n = 27 Acute ischaemic stroke within 6 h of ictus	Randomised to receive 900,000 units urokinase via intravenous (n = 14) or intra-arterial (n = 13) routes.	Study terminated prematurely because 7/27 patients (26%) died (4 in the intravenous group and 3 in the intra-arterial group). No significant difference in proportion of patients with mRS ≤ 2, mortality or frequency of symptomatic ICH between treatment groups. Average treatment times were significantly shorter in the intravenous (4 h 16 min) vs intra-arterial group (5 h 24 min; p = 0.007).	The trial was too small to provide any conclusions.
Macleod et al. [24]	n = 16 Acute ischaemic stroke due to occlusion of the basilar or vertebral arteries within 24 h of ictus. Glasgow Coma Scale ≥ 9	Randomised to receive intra-arterial urokinase plus heparin/warfarin anticoagulation (n = 8) or heparin/warfarin anticoagulation (n = 8).	4/8 patients who received intra-arterial urokinase compared with 1/8 patients in the control group were not dead or disabled (combined Barthel and Rankin scores and mortality) at 6 months (OR: 0.14 (0.02–1.43); p = 0.28). Among survivors, median mRS was 1 in the urokinase group and 3 in the control group.	Results supported the need for a large-scale trial to establish the efficacy of intra-arterial thrombolysis for acute basilar artery occlusion.
MELT [25]	n = 114 Acute MCA territory occlusion within 6 h of ictus NIHSS ≤ 22	Randomised to receive intra-arterial urokinase (n = 57) or placebo (n = 57).	Study terminated prematurely after approval of intravenous infusion of alteplase in Japan. Non-significant increase in proportion of patients with 90 day mRS < 2 (primary endpoint) (49% vs 39%; p = 0.44) but significant increase in 90-day mRS ≤ 1 (42% vs 23%; p = 0.045) in those treated with urokinase vs placebo. No significant difference in 90-day mortality (5% vs 4%; p = 1) and 24-hour ICH (9% vs 2%; p = 0.206) between patients treated with urokinase vs placebo.	The trial was aborted prematurely and the primary endpoint did not reach statistical significance. Nevertheless, the secondary analyses suggested that intra-arterial thrombolysis may increase the likelihood of excellent functional outcome.
SYNTHESIS pilot [26]	n = 54 Acute ischaemic stroke within 3 h of ictus for intravenous therapy and within 6 h of ictus for intra-arterial therapy NIHSS ≤ 25	Randomised to receive 0.9 mg/kg (maximum 90 mg) alteplase intravenously within 3 h (n = 29) or intra-arterially within 6 h (with additional intravenous heparin, mechanical clot disruption and/or retrieval if necessary) (n = 25).	Increased proportion of patients with 90 day mRS ≤ 1 (48% vs 28%; p = 0.067 in those treated with intra-arterial vs intravenous thrombolysis). No significant difference in mortality (20% vs 14%) or symptomatic ICH (14% vs 8%) between patients treated with intra-arterial vs intravenous thrombolysis. Median treatment times were significantly shorter in the intravenous (2 h 35 min) vs intra-arterial group (3 h 15 min; p < 0.001).	Intra-arterial thrombolysis is a safe and feasible alternative to intravenous thrombolysis in acute ischaemic stroke.
SYNTHESIS expansion [27,28]	n = 362 Acute ischaemic stroke within 4.5 h of ictus	Randomised to receive 0.9 mg/kg (maximum 90 mg) alteplase intravenously (n = 181) or intra-arterially (with additional intravenous heparin, mechanical clot disruption or retrieval or a combination of these approaches) (n = 181).	No significant difference in 90-day mRS ≤ 1 (30% vs 35%), mortality (26% vs 18%) or 7-day symptomatic ICH (6% vs 6%) between patients treated with intra-arterial vs intravenous thrombolysis. Median treatment times were significantly shorter in the intravenous (2.75 h) vs intra-arterial group (3.75 h; p < 0.001).	Endovascular therapy incorporating intra-arterial thrombolysis is not superior to standard treatment with intravenous thrombolysis for acute ischemic stroke.

functional outcome with intra-arterial thrombolysis and studies that compared intra-arterial and intravenous treatment showed intra-arterial treatment times to be significantly longer. Sample sizes ranged from 8 to 362 (mean 113; median 54) and studies differed in their inclusion and exclusion criteria, interventional strategies and primary and secondary outcomes. It is also important to note that patients in both intervention and control arms of a number of the trials received intravenous heparin infusions. Whilst the PROACT studies were undertaken in the late 1990s, no further RCTs of intra-arterial thrombolysis were published until 2005. Over this time-frame, there were considerable advances in acute stroke treatment and this is borne out by the premature termination of the MELT trial, when intravenous alteplase treatment was approved in Japan, and the range of interventional options employed in more recent trials. It is also worth noting that in the PROACT trials, less than 4% of patients screened were randomised [22,29]. On the basis of the RCTs' findings, especially PROACT II, international guidelines have recommended intra-arterial thrombolysis as an option for treatment of selected patients who have major stroke of less than 6 h duration due to occlusion of the MCA and who are not otherwise candidates for intravenous thrombolysis, on the basis of contraindications [30,31].

2.2. Combined intravenous and intra-arterial thrombolysis

Studies have shown that patients with recanalised vessels have improved clinical outcome and that endovascular approaches have superior reperfusion outcomes compared with intravenous thrombolysis. Indeed, in a study of 223 patients with large vessel occlusion, Rai et al. showed endovascular therapy to achieve a significantly higher odds of a favourable outcome (3-month mRS ≤ 2) compared with intravenous thrombolysis (44.7% versus 26%; OR 2.3 (95% CI: 1.3–4.1); $p = 0.003$) with no difference in mortality or haemorrhage [32]. However, clinical benefit may be counterbalanced by delays to initiating treatment via an intra-arterial approach with thrombolytic and recanalisation studies demonstrating that the effectiveness of these therapies is time-dependent [33]. The concept of combining the advantages of intravenous thrombolysis (speed of and certainty of initiation of therapy as well as widespread availability) and intra-arterial recanalisation therapy (titrated dosing, mechanical aids to recanalisation, and the potential for superior and earlier recanalisation) was initially evaluated in the EMS and IMS trials [34,35]. In these trials, intravenous alteplase was administered within 3 h of symptom onset at a dose of 0.6 mg/kg and then a maximum of 20 mg (in EMS) or 22 mg (in IMS) was subsequently administered intra-arterially. Combined intravenous and intra-arterial treatment was shown to provide improved outcomes compared with placebo and improved rates of recanalisation compared with intravenous thrombolysis (55% versus 10%). However, combined treatment resulted in similar rates of neurological outcome, symptomatic haemorrhage and mortality compared with intravenous thrombolysis alone and there were higher rates of asymptomatic haemorrhage and procedural complications [34,35]. These results were replicated in case series in other centres and led to the design of further trials in the field [36–39].

The IMS investigators proceeded to investigate further a combined intravenous and intra-arterial approach to recanalisation in the IMS II and III studies [33,40]. In the IMS II study, 81 ischaemic stroke patients received intravenous and intra-arterial alteplase as per IMS trial methodology but patients also received endovascular intervention with the EKOS system (consisting of a micro-infusion catheter with an ultrasound element at the distal tip) [33,41]. The IMS II trial showed similar results to its forerunner, IMS, with 90-day mRS ≤ 1 and mortality rates being 33% and 16% respectively that the triallists compared with 32% and 21% respectively in the treatment arm and 18% and 24% respectively in the placebo arm of the NINDS trial [3,33]. Symptomatic haemorrhage rate was 9.9%, not significantly different from 6.6% in the NINDS trial patients who received intravenous thrombolysis, but asymptomatic haemorrhage rate was 32.1% compared with 6.0% in the NINDS trial patients who received intravenous thrombolysis.

In the IMS II trial, 60% of patients achieved TIMI ≥ 2, similar to the rate of reperfusion in PROACT II [22]. However, the difficulty in comparing reperfusion in the IMS II trial with other endovascular trials without prior intravenous thrombolysis is that intravenous thrombolysis has been shown to achieve complete recanalisation of occluded major intracranial arteries in 13–21% of patients within 30–60 min [42,43]. Such recanalisation may include complete re-opening or even fragmentation and distal embolisation of clots that were initially more proximal. In IMS II, the clots treated intra-arterially had yet to respond or had responded incompletely to intravenous thrombolysis, but some patients had been already recanalised intravenously without the need for additional therapy. Thus, the reperfusion rates reported in the IMS I and II trials may underestimate the true reperfusion rate of the combined intravenous/intra-arterial approach [33]. Furthermore, total doses of alteplase used in the EMS, IMS and IMS II studies (80–82 mg) were lower than those in the landmark trials of intravenous thrombolysis (90 mg). In order to investigate this area further, the IMS III trial randomised 656 patients to combination treatment (434 patients) or intravenous thrombolysis alone (222 patients) with intravenous treatment being initiated in all patients within 3 h of stroke onset and at a dose of 0.9 mg/kg (up to a maximum of 90 mg). If an appropriate thrombus was identified angiographically, endovascular treatment continued, within 5 h of symptom onset, with the choice of endovascular strategy being made by the treating neurointerventionalist [40]. The trial was stopped early because of 'futility' with similar functional independence (90-day mRS ≤ 2: 40.8% with endovascular therapy versus 38.7% with intravenous therapy) and mortality outcomes (19.1% with endovascular therapy versus 21.6% with intravenous therapy) in the two treatment groups [40]. The trial had difficulty recruiting patients because interventional mechanical endovascular treatment became widespread at the time such that many physicians who were treating patients with acute stroke felt that the "answer was in" and, as such, treatment equipoise was lost [44]. Furthermore, significant reimbursement was available in the USA for employment of endovascular devices.

In addition to the IMS investigators' results, a number of other studies have demonstrated the feasibility and safety of combined treatments for acute ischaemic stroke involving both intravenous and intra-arterial interventions [36,45–47]. Nogueira et al. showed that rates of symptomatic haemorrhage were similar whether the bridging dose of intravenous alteplase was 0.6 or 0.9 mg/kg [45].

2.3. Endovascular mechanical thrombolysis and clot retrieval

The limitations of intravenous and intra-arterial thrombolysis as well as the desire to achieve improved recanalisation rates and functional outcomes prompted the development and evolution of mechanical interventional endovascular treatment strategies for acute ischaemic stroke. In the beginning, several treatment options were attempted, including clot-retrieval. All early investigations focussed on vessel recanalisation (assessed by the TIMI and/or TICI scoring systems (Box 1)) [48].

2.4. MERCI, Penumbra aspiration and stent-retrieval devices

The endovascular devices attracting most interest both from a clinical and investigative standpoint have been the MERCI, Penumbra aspiration and stent-retriever devices. The MERCI device consists of a flexible tapered wire with 5 helical loops that can be embedded within the thrombus for retrieval. The MERCI study examined its use in 151 patients with ischaemic stroke secondary to large vessel occlusion, who had a contraindication to intravenous thrombolysis, within 8 h of symptom onset [49]. Recanalisation, defined as TIMI ≥ 2, was achieved in 46% of patients and good neurological outcome (90-day mRS ≤ 2) was achieved in 28% of patients. However, in those patients with successful

Box 1
Scoring systems for angiographic assessment of cerebral blood flow.

Thrombolysis in myocardial infarction (TIMI) score

- TIMI 0 flow (no perfusion) refers to the absence of any antegrade flow beyond a coronary occlusion
- TIMI 1 flow (penetration without perfusion) is faint antegrade coronary flow beyond the occlusion, with incomplete filling of the distal coronary bed
- TIMI 2 flow (partial reperfusion) is delayed or sluggish antegrade flow with complete filling of the distal territory
- TIMI 3 flow (complete perfusion) is normal flow which fills the distal coronary bed completely.

Thrombolysis in cerebral infarction (TICI) score

- TICI 0 flow (no perfusion) refers to the absence of any antegrade flow beyond the occlusion
- TICI 1 flow (penetration without perfusion) refers to contrast penetration past the initial obstruction but with minimal filling of the normal territory
- TICI 2a flow (partial perfusion) with incomplete distal branch filling of <50% of the expected territory
- TICI 2b flow (partial perfusion) with incomplete distal branch filling of ≥ 50%–99% of the expected territory
- TICI 2c flow (near complete perfusion) without clearly visible thrombus but with delay in contrast run-off
- TICI 3 flow (complete perfusion) is normal filling of all distal branches of the expected territory in a normal haemodynamic fashion.

recanalisation, good neurological outcome (46% versus 10%) and mortality (32% versus 54%) were significantly improved compared with patients without recanalisation. Intra-arterial thrombolysis was allowed in cases of treatment failure with the device or to treat distal embolus not accessible to the device after successful proximal embolectomy. Intravenous heparin was also allowed at the discretion of the investigator. Procedural complications occurred in 13% of patients, of which over half were clinically significant. These included vascular perforations leading to subarachnoid haemorrhage that accounted for 45% of the symptomatic ICH occurring in 7.8% of patients [49]. Improved results (57% recanalisation rate and 36% patients achieving 90-day mRS ≤ 2) were seen in the subsequent Multi MERCI trial that tested a newer generation MERCI device and allowed prior intravenous thrombolysis (in 29% of patients) [50], and the combined results of the MERCI and Multi MERCI trials showed that patients with isolated M2 occlusions were revascularised at a higher rate and with fewer passes than those with M1 lesions [51]. Josephson et al. compared outcomes in 149 patients enrolled in the MERCI and Multi MERCI trials who would have been eligible for inclusion in the PROACT II trial, with the results of PROACT II and found rates of good outcome and mortality to be similar [52].

The Penumbra aspiration device incorporates a reperfusion catheter and separator. The reperfusion catheter is used in parallel with the separator and an aspiration source to separate the thrombus and aspirate it from the occluded vessel. The safety of the Penumbra system was assessed by Bose et al. in 23 ischaemic stroke patients with an angiographically verified large vessel occlusion presenting within 8 h of symptom onset who were ineligible or refractory to intravenous thrombolytic treatment. All patients received systemic anticoagulation and general anaesthesia peri-procedure, and 45% of patients received adjunctive intra-arterial thrombolysis. Recanalisation, defined as TIMI ≥ 2, was achieved in 100% of vessels and a good neurological outcome, defined by ≥4 point improvement in hospital discharge NIHSS score or 30-day mRS ≤ 2 was achieved in 45% of patients. All-cause mortality rate was 45%. None of the deaths were related to the study device and the mortality rate was deemed by the authors to be lower than expected in a cohort of patients where 70% had a baseline NIHSS score >20 or basilar occlusion. Procedural complications occurred in 9.5% of patients and 35% of patients, of whom 87.5% had received additional lytic therapy, experienced ICH [53]. The Penumbra system was further evaluated in the Penumbra Pivotal Stroke Trial in 125 ischaemic stroke patients with an angiographically verified large vessel occlusion presenting within 8 h of symptom onset who were ineligible or refractory to intravenous thrombolytic treatment [54]. All patients received systemic anticoagulation and general anaesthesia peri-procedure and 10% of patients received adjunctive intra-arterial thrombolysis. Recanalisation, defined as TIMI ≥ 2, was achieved in 81.6% of patients and a good neurological outcome, defined by ≥4 point improvement in hospital discharge NIHSS score or 30-day mRS ≤ 2, was achieved in 41.6% of patients. In those patients with successful recanalisation, 32% of patients achieved a discharge NIHSS of 0–1 or improvement by ≥10 compared with 5% in patients without recanalisation. Overall 90-day mRS ≤ 2 and all-cause mortality were 25% and 32.8% respectively with trends to improvement with recanalisation (29% versus 9% for mRS ≤ 2 and 29% versus 48% for mortality). Procedural complications occurred in 12.8% of patients, of which 2.4% were rated as serious [54]. 28% of patients, of whom a third had received additional lytic therapy, experienced ICH of which 11.2% were symptomatic and 16.8% were asymptomatic.

The subsequent POST trial in 157 patients demonstrated improved outcome with Penumbra device use with an 87% recanalisation rate to TIMI ≥ 2; 41% of patients achieving mRS ≤ 2 at 90-day follow-up and all-cause mortality being 20%. Patients who were successfully revascularised by the Penumbra system again had significantly better outcomes than those who were not [55]. Further small studies with the device confirmed these findings with recanalisation rates of 72–100% [56–59]. More recently, Psychogios et al. demonstrated successful recanalisation with the Penumbra system to be associated with significant improvement of functional outcome in patients experiencing ischaemic stroke secondary to anterior but not posterior circulation occlusions [60].

In 2005–2006, stent-assisted recanalisation was studied as an alternative to target areas of cerebrovascular occlusion [48,61,62]. In 2009, the SARIS trial evaluated the safety of intracranial stenting as a primary therapeutic intervention for acute ischaemic stroke within 8 h of symptom onset in 20 patients with angiographic demonstration of focal intracerebral artery occlusion and either contraindication to or failure to improve 1 h after intravenous alteplase administration. All patients were successfully revascularised although 60% required the use of an adjuvant pharmacological infusion (of eptifibatide or alteplase) or angioplasty. The risk of asymptomatic and symptomatic haemorrhage was 10% and 5% respectively and no procedure-related complications were reported. At 1-month follow-up, mRS ≤ 3 was achieved in 12 of 20 (60%) patients and mRS ≤ 1 was achieved in 9 of 20 (45%) patients [63].

Subsequently, devices that employed stenting and clot retrieval to yield rapid flow restoration in acute cerebral ischaemia were evaluated. Miteff et al. investigated the safety and capability of the Solitaire stent-retriever device in 26 patients presenting with proximal cerebral vessel occlusion and demonstrated recanalisation (TIMI ≥ 2) with Solitaire thrombectomy as the single treatment technique in 16 patients and in combination with urokinase or the Penumbra device in 9 of the remaining 10 patients. A favourable clinical outcome (mRS ≤ 2) was seen in 3 of 5 patients with MCA occlusion, 6 of 11 patients with ICA occlusion, and 2 of 10 patients with basilar artery occlusion. Two patients had symptomatic ICH [64]. Subsequent single and multi-centre studies, each investigating more than 100 acute large vessel stroke patients treated with the Solitaire stent as the first-line device to restore blood flow, demonstrated recanalisation (TIMI ≥ 2 or TICI ≥ 2b) in over 75% of patients and good outcome (90-day mRS ≤ 2) in at least 55% of patients. Symptomatic ICH rates were <8% and up to 20% of patients

died or were lost to follow-up [65–67]. Procedure time appears to be a critical determinant of outcome with unfavourable outcome being associated with longer procedure times [68]. Koh et al. showed procedure time to vary between 37 and 96 min in 10 studies of mechanical thrombectomy with Solitaire stent retrieval for acute ischaemic stroke [69] and Dorn et al. found the number of required Solitaire passes to range between 1 and 12 (mean 2.46; median 2) [66].

Single centre studies investigating up to 60 patients have also showed the Trevo stent-retriever device to be effective, either as monotherapy or in combination with intra-arterial thrombolysis, for large-vessel stroke lasting <8 h in the anterior circulation or <12 h in the vertebrobasilar circulation [70,71]. Mendonca et al. demonstrated successful revascularisation (TICI ≥ 2a) in 77% of patients and good outcome (90-day mRS ≤ 2) in 30% of patients [70]. San Román et al. demonstrated successful recanalisation (TICI > 2b) in 73.3% of patients when only the Trevo device was used and in 86.7% when other devices or additional intra-arterial thrombolysis was used, and good outcome (90-day mRS ≤ 2) in 45% of patients [71]. Symptomatic ICH rates were <12% but mortality rates were 28–30% in these studies [70,71].

In a head-to-head prospective study comparing the outcome of 33 patients with an angiographically verified occlusion of the anterior cerebral circulation, Mendonca et al. showed no significant differences between the Trevo and Solitare devices with rates of revascularisation being 77% and 60%, and good functional outcome being 38% and 40%, respectively [72]. However, RCTs have demonstrated both the Solitaire and Trevo devices to be significantly superior to the MERCI device for the endovascular treatment of acute stroke within 8 h of symptom onset [73,74]. In the SWIFT study of 113 patients from 18 sites across the USA and Europe, compared with MERCI, the Solitaire device achieved improved rates of recanalisation of TIMI > 2 (61% versus 24%) and 3-month outcome of mRS ≤ 2 (58% versus 33%) [73]. In the TREVO 2 trial in 88 patients from 26 sites across the USA and Europe, compared with MERCI, the Trevo device achieved improved rates of recanalisation of TICI > 2 (86% versus 60%) [74]. These findings led the triallists to suggest that patients with large vessel occlusion strokes ineligible for (or refractory to) intravenous thrombolysis should be treated with a stent-retriever in preference to a MERCI device [74]. Broussalis et al. replicated the superior results of stent-retrievers compared with MERCI devices in a larger non-randomised study in 122 patients that showed improved rates of recanalisation of TICI ≥ 2b (82% versus 62%) and 3-month outcome of mRS ≤ 2 (65% versus 35%). In addition, significantly shorter treatment times (72 versus 122 min) and reduced rates of ICH (10% versus 28%) were demonstrated [75]. Furthermore, a meta-analysis of 16 observational studies involving 925 patients showed average recanalisation rates to be 59.1% with MERCI, 86.6% with Penumbra and 92.9% with stent-retrievers; and functional independence (mRS ≤ 2) to be achieved in 31.5% of patients in MERCI studies, 36.6% in Penumbra studies, and 46.9% in stent-retriever studies [76].

2.5. Limitations of endovascular treatment

Whilst all hyperacute stroke patients require specialist multidisciplinary care [77], individuals treated with endovascular approaches generally require special additional attention in the post-procedural period [78]. Important measures include monitoring of vital signs including assessment for vagal symptoms of bradycardia and hypotension (due to pain from pressure on a large artery). Assessment of the arterial puncture site for bleeding, pain, tenderness, swelling, or haematoma, and preservation of the peripheral circulation distal to the arterial access site is also crucial. Indeed, the most frequent complications of interventional treatment are related to the arterial access site [79] with the prevalence of these complications ranging between 1% and 17% [78]. Patients also need to be monitored to help decrease preventable complications such as contrast-induced nephropathy and allergic reactions [80]. With appropriate patient selection, attention to technical details and meticulous post-procedural care, such complication rates may be minimised [81]. Standardisation of endovascular treatment protocols, however, may be difficult due to varying patient characteristics. Other cited potential disadvantages of endovascular therapy include vascular injury at the site of intervention, distal clot fragmentation, an alteplase-induced increase in blood–brain barrier permeability and lack of expertise [49,82,83]. Furthermore, there is a paucity of RCTs' data for endovascular interventions, with studies often using data from other trials for comparison, and a lack of 'cost-benefit' economic evaluations.

Studies have shown that symptom onset to treatment time is longer for endovascular therapy compared with intravenous thrombolysis [84]. Endovascular therapy in itself does not have increased symptom onset to treatment time but, in contrast to intravenous reperfusion therapy, endovascular approaches require a multi-professional infrastructure involving additional personnel from a number of disciplines including interventional neuroradiology and catheter laboratory support staff. Inadequate setup of these resources leads to the reported delays in endovascular treatment times. A recent UK study showed that the number of hospitals equipped with multi-disciplinary teams to provide such treatment is limited [83]. A number of possible solutions have been suggested including the involvement of vascular interventional radiologists or interventional cardiologists to undertake endovascular stroke therapy in addition to interventional neuroradiologists and/or organisation of regional stroke networks with a hub and spoke model [83,85,86]. In support of the latter, studies have shown showed that 'high-volume' centres undertaking increased rates of endovascular therapy had faster times to treatment, higher reperfusion rates and higher rates of good clinical outcomes [65,87].

2.6. Patient selection

Endovascular treatments for acute ischaemic stroke have developed to achieve very high rates of recanalisation but clinical outcome does not depend on recanalisation alone. In addition to the significantly increased treatment times with endovascular intervention that may limit successful reperfusion of viable brain tissue, a number of studies have shown increased age and NIHSS score to be associated with worse clinical outcome [88–90]. Chandra et al. showed that, despite comparable rates of reperfusion and haemorrhage, patients aged >80 had worse clinical outcomes and suggested that increased vessel tortuosity (delaying reperfusion), reduced neurological reserve and a higher incidence of medical comorbidities and post-stroke complications may be contributory [90].

More recently, studies have been undertaken to investigate if pre-treatment brain imaging may help predict patient outcome. The START trial showed higher ASPECTS (Alberta Stroke Programme Early CT Score) on pre-treatment CT-angiogram source images to be significantly associated with good outcomes (mRS ≤ 2: 21.4% for ASPECTS 0–4, 55.9% for 5–7, and 62.5% for 8–10; $p = 0.08$) and, adjusting for age and NIHSS, pre-treatment ASPECTS was an independent predictor of good outcome (OR 1.5, $p < 0.04$) [91,92]. A number of non-randomised studies have also evaluated the use of perfusion imaging to guide endovascular therapy demonstrating that patients with a mean transit time-cerebral blood volume mismatch who had early reperfusion after endovascular treatment had more favourable clinical outcomes [93–95]. Fargen et al. created a score based on NIHSS, age and percentage decrease in cerebral blood volume on CT perfusion imaging that strongly correlated with outcome on mRS. The score awarded 2 points for an NIHSS score of ≥15, 1 point for age ≥70 years, and 1 point for decreased cerebral blood volume of ≥50% and scores of 0, 1, 2, 3, and 4 were associated with 84%, 50%, 36%, 25%, and 8% chance of a good outcome (mRS ≤ 2) at 90 days [96]. Subsequent to these studies, the recently completed MR RESCUE trial randomised 118 patients within 8 h of the onset of large-vessel, anterior-circulation ischaemic stroke, with an NIHSS score of 6–29, to undergo mechanical embolectomy (by MERCI or Penumbra device) or

receive standard medical care (including intravenous thrombolysis) with randomisation being stratified according to whether the patient had a favourable penumbral pattern (substantial salvageable tissue and small infarct core) or a non-penumbral pattern (large core or small or absent penumbra) on brain imaging [97]. In the primary analysis of 90-day functional outcome, there was no interaction between the pre-treatment imaging pattern and treatment assignment, and the mean mRS was 3.9 in both embolectomy and standard care patient groups. Rates of mortality and symptomatic ICH were also similar across patient groups [97]. The triallists noted that a low rate of revascularization in the embolectomy group, an extended time from imaging to embolectomy and heterogeneity of imaging approaches may have contributed to the neutral results [97]. Furthermore, the neutral results in the MR RESCUE study were consistent with analyses of perfusion-imaging based intravenous thrombolysis RCTs that showed thrombolysis after 3 h after ictus in mismatch patients not to improve clinical outcome [98,99].

3. Conclusion

Stroke used not to be considered as a medical emergency but this nihilistic perception has been changed by evidence of the effectiveness of interventions for acute ischaemic stroke [100]. Based on the evidence from RCTs, current guidelines recommend intravenous thrombolysis for acute ischaemic stroke up to 4.5 h after symptom onset and intra-arterial thrombolysis as a treatment option for acute MCA occlusion within a 6 h window and for acute basilar occlusion in selected patients. RCTs have not been able to demonstrate superiority of endovascular treatment against intravenous thrombolysis within 4.5 h but endovascular treatment is approved for patients in whom intravenous thrombolysis is contraindicated or for rescue treatment after failed intravenous thrombolysis. In view of the lack of randomised data for mechanical thrombectomy devices, in the United Kingdom these are advised to be considered as part of institutional protocols and with conformation to high standards of clinical governance as part of thrombectomy registries [30,31,52,101,102].

Over the last decade there has been a tremendous evolution of endovascular options with several different modalities now available. Despite a lack of randomised data and the risk of peri-procedural complications, a range of endovascular modalities have been shown to be safe with improved rates of recanalisation and clinical outcome for large vessel strokes [32]. Indeed, a recent meta-analysis of 32 studies involving 1113 patients showed endovascular therapy to achieve rates of recanalisation and favourable outcome of 79% (95% CI: 73–84) and 40% (95% CI: 34–46) respectively [103]. This data confirms that recanalisation does not necessarily lead to improved clinical outcome which appears to be governed more by the time from ictus to intervention. Whilst early studies employed intra-arterial thrombolysis or mechanical modalities as separate therapeutic options, more recently, combined therapy has been advocated to optimise the chances of recanalisation; although many centres now use endovascular therapy as a standalone treatment to avoid complications associated with lysis. Most certified or active stroke centres are now using mechanical thrombectomy with aspiration or stent-retrievers for proximal lesions and intra-arterial thrombolysis for distal occlusions or inaccessible clots. Pragmatic, multi-centre, randomised studies are underway to explore further the benefits of endovascular treatment whilst, at the same time, novel devices and imaging-based predictors of successful outcome are under investigation [104]. New trials, recruiting from experienced centres, are focusing on new mechanical techniques and optimising delays between different steps of the treatment pathway.

Conflict of interests

The authors state that they have no conflicts of interest.

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