Review

Cerebrovascular Diseases

Cerebrovasc Dis 2016;42:170–177
DOI: 10.1159/000445449

Received: January 25, 2016
Accepted: March 11, 2016
Published online: April 26, 2016

Endovascular Stroke Management: Key Elements of Success

Nathan W. Manning[a, b] René Chapot[c] Philip M. Meyers[a]

[a]Department of Radiology and Neurological Surgery, College of Physicians and Surgeons, Columbia University, New York, N.Y., USA; [b]Florey Institute of Neuroscience and Mental Health, University of Melbourne, Parkville, Vic., Australia; [c]Department of Intracranial Endovascular Therapy, Alfried-Krupp Krankenhaus Hospital, Essen, Germany

Key Words
Ischaemic stroke · Penumbra · Reperfusion · Thrombolysis · Endovascular · Stent-retriever · Thrombectomy

Abstract
Background: In the last 12 months, treatment of acute ischaemic stroke secondary to large vessel occlusion has undergone a paradigm shift. The success of endovascular surgery, and in particular, the use of stent-retrievers, is remarkable. ***Summary:*** Beyond percentages and p values, the endovascular trials demonstrated, in their similarities and their differences, the critical elements of successful intervention in acute ischaemic stroke. Patient selection based on non-invasive neuroimaging has emerged as a critical step in acute ischaemic stroke management. The more sophisticated imaging-based selection, those assessing collateral blood flow or ischaemic penumbra appear to be associated with better outcomes and possibly fewer complications. The importance of achieving effective, quality reperfusion is also demonstrated, in a remarkably linear fashion, across the 5 published trials. This may emerge as the single most important determinant of functional outcomes. While reperfusion may succeed time as the preeminent modifiable variable, it remains clear that achieving quality reperfusion in a timely manner should remain the goal of all acute stroke programs. ***Key Message:*** Comparing the recent successful endovascular stroke trials, both between one another, and to their unsuccessful predecessors, emphasizes the importance of patient selection, time and reperfusion. Highlighting these factors allows for a better understanding of the challenges facing clinicians and the changes required to be made in hospital systems in order to achieve a new standard of care in treating acute ischaemic stroke.

Introduction

There are now three eras in the evolution of acute ischaemic stroke management. The first era introduced stroke-specific supportive care and developed the specialized stroke unit. The second era, which lasted for 20 years, introduced moderately effective reperfusion therapy with the use of intravenous thrombolysis. The recently arrived third era, delivers highly successful reperfusion therapy

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Nathan W. Manning
Department of Neurological Surgery
College of Physicians and Surgeons, Columbia University
New York, NY 10032 (USA)
E-Mail dr.nathan.manning@gmail.com

with the refinement of mechanical thrombectomy. The success of 5 randomized control trials, MR CLEAN, REVASCAT, ESCAPE, SWIFT-PRIME and EXTEND-IA demonstrated the overwhelming efficacy of endovascular reperfusion therapy using stent-retriever devices [1–5]. The introduction of highly effective stent-retrievers allowed these trials to achieve a critical level of reperfusion necessary to achieve remarkable improvements in functional outcomes. These studies also demonstrate the potential of neuroimaging-based patient selection to refine patient selection and reduce complications.

The importance of reperfusion has been demonstrated in the setting of intravenous tissue plasminogen activator (IV-tPA) in the DEFUSE and EPITHET studies [6–10]. This was further investigated in DEFUSE-2 with the use of intra-arterial tPA and penumbral imaging [11–13]. The recent successful endovascular trials demonstrate the importance of timely, quality reperfusion of the ischaemic penumbra [14]. They have now established endovascular mechanical thrombectomy as the treatment of choice for ischaemic stroke secondary to a large vessel occlusion. By grouping the recent trials on the basis of their similarities, it is possible to further explore the relative importance of the role of timing, imaging-based selection and reperfusion compared both to these successful trials and to the previous trials that failed to demonstrate benefit. This not only sheds light on the mechanisms behind the failure of previous studies but also points to a necessary hierarchy of reperfusion, time and selection critical to replicate trial success in the general stroke population. The success of these trials should not only be the basis of guideline reform, but also the basis to provide focus on the critical pathophysiology and treatment priorities in each and every acute ischaemic stroke patient.

MR CLEAN and REVASCAT [2, 4]

The 2 European studies provide the simplest approach to successful endovascular management of acute ischaemic stroke. Enrolling 500 patients at 16 centres across the Netherlands, MR CLEAN demonstrated a 13.5% absolute difference in functional outcomes favouring endovascular surgery over standard care (OR 2.16). The presentation of the MR CLEAN results prompted the review and subsequent premature termination of the 4 other major trials including REVASCAT from Catalonia, Spain, which had recruited 206 of a planned 690 patients.

Both MR CLEAN and REVASCAT achieved modest results in terms of functional outcomes in comparison to previous series [15, 16] and to previous interventional trials [17, 18]. Combining both studies, good functional outcomes (mRS 0–2) were achieved in 36.0% of patients randomized to intervention and only 21.6% of patients randomized to standard care. This is partly due to the broad inclusivity of the trials. Patients were enrolled if they could undergo intra-arterial treatment within 6 h of symptom onset for MR CLEAN and up to 8 h for REVASCAT. This meant that some late-presenting patients were enrolled beyond the time window to receive IV-tPA. This would be expected to decrease rates of functional independence, particularly in light of the severe stroke population studied (confirmed large vessel occlusion; median NIHSS 17) [17, 19]. Given that 89.0% of patients received IV-tPA prior to randomization in MR CLEAN and 72.8% in REVASCAT, there is likely to be some downward effect on functional independence compared to previous trials [17, 18]. The use of imaging to confirm a large vessel occlusion, which was largely missing from previous studies, would also be expected to exert downward pressure on functional outcomes. This makes direct comparisons with the SYNTHESIS expansion trial challenging. SYNTHESIS expansion did not use vascular imaging to confirm a target lesion prior to enrollment [18]. Therefore, it is unknown what stroke population was investigated in SYNTHESIS, as it likely included patients without a large vessel occlusion, and the utility of that trial remains unclear. Vascular imaging was more common in IMS-III, which also employed a clinical cut-off (NIHSS >9) in patients in whom vascular imaging could not be performed. Functional independence was achieved in 40.8% of IA patients and 38.7% IV-tPA patients in IMS-III [17]. A previous retrospective study explored outcomes in patients with confirmed large vessel occlusion receiving IV-tPA. In this population, treatment with IV-tPA achieved good functional outcomes in 35.0% [16]. The relatively low rates of functional independence achieved in MR CLEAN and REVASCAT, particularly for patients randomized to standard care may at first be startling. However, viewed in proper context, they are the most encouraging messages from these trials and speak to the generalizability of the results.

Previous interventional stroke studies have experienced a serious limitation in terms of very poor rates of recruitment. In DEFUSE-2, average patient enrollment was only 5.1 per site per year and in MR RESCUE only 0.8. This likely reflected a lack of clinical equipoise [14]. All Dutch centres offering endovascular stroke surgery were included in MR CLEAN and from 2013 reimbursement for endovascular stroke surgery was possible only

within the trial [2]. The REVASCAT study was embedded in a reperfusion registry, analysis of which revealed only 8 patients who were eligible for endovascular surgery but not included in the trial. The highly successful recruitment and the permissive inclusion criteria resulted in a remarkably severe and broadly representative patient population reflected in the relative distribution of vascular lesions. Occlusions involving the ICA and M1 segments simultaneously were seen in 26.6% of patients across the 2 studies [2, 4]. This has previously been demonstrated to be both a predictor of IV-tPA nonresponse and poor clinical outcomes [20–22], due to the relatively larger clot burden and relatively poor collaterals seen in such lesions [23, 24]. In addition to high rates of dual segment intracranial lesions, both studies also demonstrated high proportions of ipsilateral cervical carotid disease (26.5%). This is markedly higher than the incidence of symptomatic extracranial ICA lesions in a large, contemporary European study [25]. Patients with tandem extracranial–intracranial occlusions typically have poorer outcomes when treated with either IV-tPA or endovascular surgery compared to patients with isolated intracranial disease, and undergo more adverse events [26–30].

Both MR CLEAN and REVASCAT demonstrate longer delays from stroke onset to groin puncture than some previous trials, at 260 and 269 (median) minutes respectively. These exceed those of both SYNTHESIS expansion and IMS-III at 225 and 196 (median) minutes respectively [31]. The delays from stroke onset to intervention suggest that the failure of the 2 older trials to demonstrate benefit is unlikely to be related solely to time delays [14], implying that time should not be given undue pre-eminence when considering stroke treatment pathways.

The MR CLEAN and REVASCAT studies offer a simple demonstration of the fundamental approach to acute ischaemic stroke: identify target vessel occlusion and achieve quality reperfusion [14]. The broad inclusion criteria allow remarkable generalizability of the results. In spite of their modest results in comparison to contemporary trials, they should provide clinicians the utmost reassurance that is needed. Using very simple and permissive inclusion criteria, they demonstrated a clear advantage to the addition of endovascular surgery to standard care for ischaemic stroke secondary to large vessel occlusion. All acute ischaemic stroke patients require urgent imaging, not only to exclude haemorrhage but also to identify a target vessel occlusion, which would thus make them potential candidates for endovascular surgery. This is now the minimum work-up required and hospital systems need to be adjusted to provide this as a priority.

ESCAPE [5]

The multicentre, international study, based in Calgary, Canada, focused its efforts on speed to intervention. A total of 316 patients underwent randomization prior to premature termination of the study. Ironically, while ESCAPE focused on delivering rapid endovascular surgery for patients who were selected based on neuroimaging, it allowed patients to undergo endovascular surgery up to 12 h from symptom onset (albeit with only 15.5% randomized beyond 6 h). This is the most liberal time inclusion out of any of the recent trials. The success of ESCAPE, with 53.0% of patients undergoing endovascular surgery achieving good functional outcomes compared with only 29.3% of patients randomized to standard care (75.6% of all patients received IV-tPA) demonstrated the utility of fast, efficient workflow combined with neuroimaging-based patient selection and quality reperfusion.

The importance of time to treatment has long been established for systemic thrombolysis [32] and is the basis of efforts to streamline workflow such as 'The Helsinki model' [33, 34]. A large, single-centre analysis of endovascular stroke treatment also demonstrated an effect for time when collateral status was excluded [22]. More recently, this effect has been validated on analysis of the IMS-III data set, albeit with modest effect size (r^2 = 0.05) [35]. The ESCAPE trial required efficient workflow systems once the patient arrived in the treatment hospital. Ambitious time targets were set at 60 min from the start of imaging until groin puncture and 90 min from the start of imaging until the time of first reperfusion. Review with feedback and coaching was provided on a weekly basis. This is undoubtedly reflected in the median stroke onset to groin puncture (185 min) and stroke onset to first reperfusion (241 min) times, which are the shortest out of any of the endovascular randomized controlled trials. To achieve this, consent was waived where possible (17.8%) and if patient factors, such as unfavourable vascular access or workflow factors, such as unavailability of the endovascular team, were present it was recommended that patients not be enrolled [5]. When comparing the recent trials, which included similar stroke patient populations (confirmed vessel occlusion; median NIHSS 17), a modest effect of groin puncture time and first reperfusion time on functional outcomes is seen (fig. 1 and 2). Furthermore, endovascular surgery resulted in a statistically significant reduction in mortality in the ESCAPE trial, 10.4 vs. 19.0% (p = 0.04) . Time to reperfusion has been demonstrated to influence stroke mortality [36] which may, at least in part drive this effect.

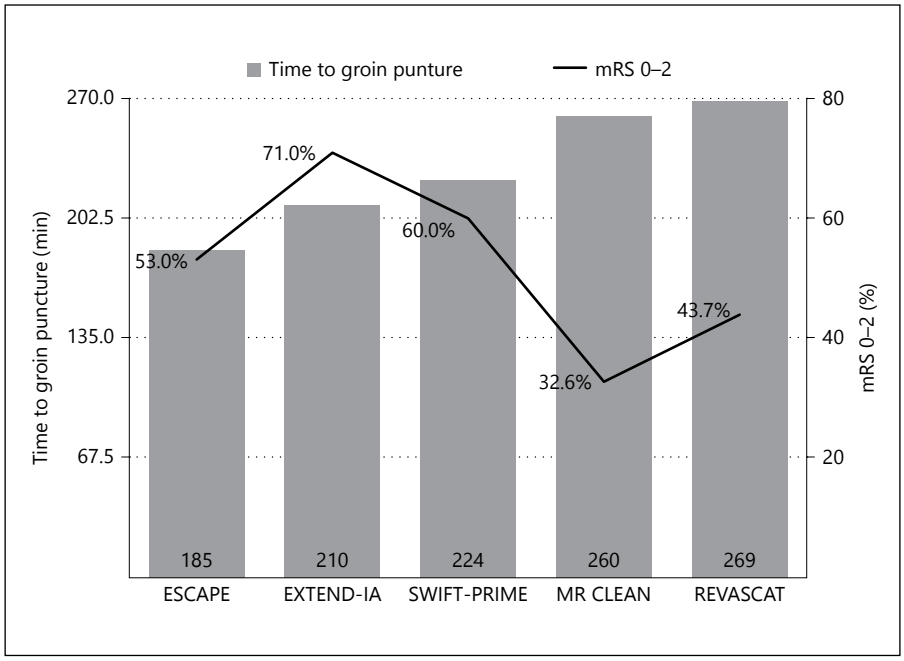

Fig. 1. Rates of good functional outcome (mRS 0–2) at day 90 stratified by the median time from stroke onset to groin puncture as reported in MR CLEAN, REVASCAT, ESCAPE, SWIFT-PRIME and EXTEND-IA.

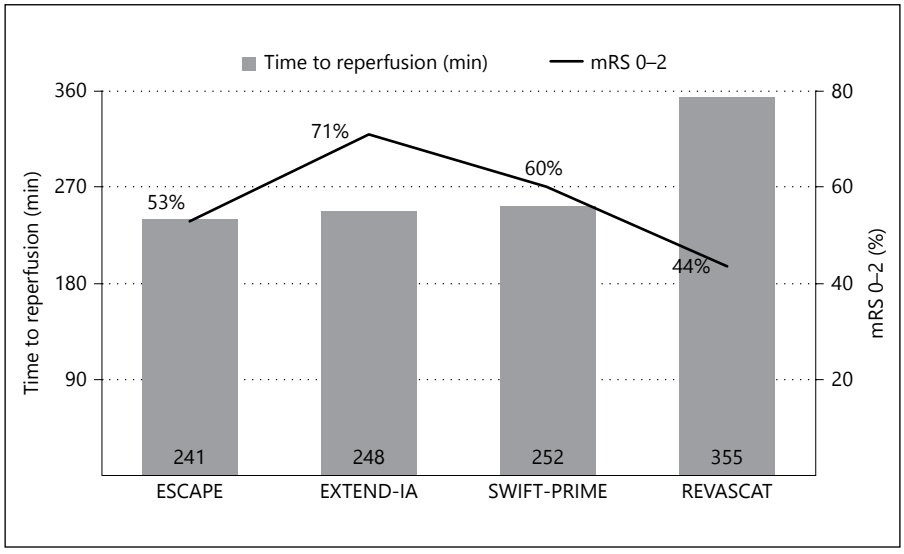

Fig. 2. Rates of good functional outcome (mRS 0–2) at day 90 stratified by the median time from stroke onset to reperfusion as reported in REVASCAT, ESCAPE, SWIFT-PRIME and EXTEND-IA.

The ESCAPE trial demonstrated marked improvements in quality reperfusion when compared to IMS-III, MR CLEAN and REVASCAT. The use of stent-retrievers and specifically the Solitare™ device (Medtronic Neurovascular, Irvine, Calif., USA) was recommended, as was the use of a balloon-guide catheter [5]. The critical importance of achieving quality reperfusion has been previously described for the IMS-III trial [14]. In recent endovascular trials, quality reperfusion appears to be of similar critical importance with regard to functional outcomes (fig. 3). In ESCAPE, endovascular surgery achieved quality reperfusion (TICI 2b/3) in 72.4% of patients, resulting in good functional outcomes in 53.0%. By comparison, standard care achieved recanalization (mAOL 2/3) on 24-hour CTA in 31.2%, resulting in good functional outcomes in 29.3% [5].

Neuroimaging has previously been demonstrated to be capable of selecting acute ischaemic stroke patients

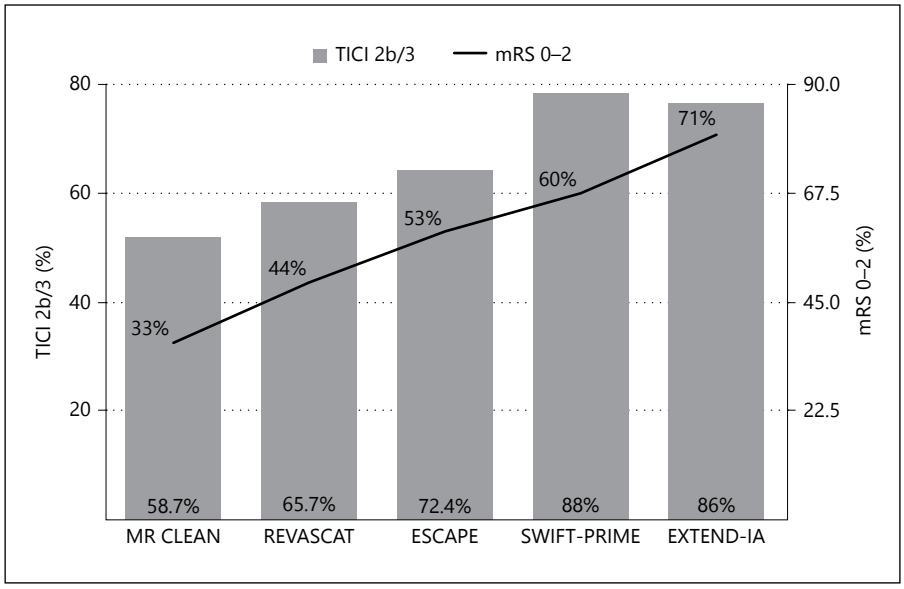

Fig. 3. Rates of good functional outcome (mRS 0–2) at day 90 stratified by TICI 2b/3 reperfusion rates as reported in MR CLEAN, REVASCAT, ESCAPE, SWIFT-PRIME and EXTEND-IA.

who will benefit most from reperfusion therapy [6–8, 11, 13, 37]. The ESCAPE trial incorporated existing techniques to estimate the ischaemic core (ASPECTS 6–10) with a novel multiphase CTA (mCTA) technique, which allowed simultaneous identification of the target vessel occlusion with a qualitative estimation of collateral channels [38]. In practice, the 3 scanning phases achieve CTA source images with different weightings. The initial CTA source images (phase 1) approximate cerebral blood flow. The final image set (phase 3) approximates cerebral blood volume, with the middle phase being an intermediate of the 2 [39]. However, rather than assessing areas of hypoperfusion, interpretation was limited to a trichotomized score of the patients' collaterals. To facilitate rapid intervention in ESCAPE, the mCTA offers the principle advantage of speed when compared to more established perfusion-imaging techniques, albeit with modest success in predicting response to treatment [38].

Achieving good functional outcomes in a majority of patients undergoing endovascular surgery, the ESCAPE trial demonstrates the success of neuroimaging in select patients who will benefit from quality reperfusion. Furthermore, it is likely that this imaging-based selection drove the statistically significant reductions in mortality observed. ESCAPE provides an important framework by which to improve workflow systems and streamline reperfusion therapy. However, given the complexity and selectivity of the workflow systems, its results may not be as generalizable as the more simple trials.

SWIFT-PRIME and EXTEND-IA [1, 3]

Enrolling patients across sites in Australia and New Zealand, EXTEND-IA is the smallest of the recent trials. It was prematurely terminated due to efficacy after enrolling 70 of the planned 100 patients. The most successful of the endovascular trials to date, EXTEND-IA demonstrated good functional outcomes in 71.0% undergoing endovascular surgery compared to 40.0% receiving IV-tPA only [3]. In spite of the small sample size, the result is strongly statistically significant ($p = 0.01$) owing to the nuanced trial design and use of penumbral imaging. The SWIFT-PRIME study, enrolling 196 patients in centres across North America and Europe delivered equivalent and equally impressive results with 60% of patients undergoing endovascular surgery achieving functional independence compared with 35% of those treated with IV-tPA alone ($p < 0.001$) [1]. Both trials share considerable commonality and taken together provide a compelling argument for the use of penumbral imaging to select patients most likely to benefit from timely, quality reperfusion of the ischaemic penumbra [14].

The exceptional rates of quality reperfusion achieved in these trials, which both exclusively used the Solitaire device, are likely critical to their success (fig. 3). Rates of TICI 2b/3 reperfusion were 87.5% for the 2 trials combined. The SWIFT-PRIME trial, in particular, achieved exceptional rates of TICI 3 reperfusion (68.7%). It is likely that the requirement of enrolling sites to have a minimum level of experience with endovascular thrombectomy procedures (40

cases) and specifically a minimum level of 20 procedures with the Solitaire device was at least partly responsible for this success. This indicates that to achieve the best level of care for stroke patients, endovascular surgery should be limited to both experienced centres and operators.

The use of penumbral imaging, specifically CT-perfusion (CTP) also appears to have been critical for the success of the 2 trials. Penumbral imaging was a strict part of the inclusion/exclusion criteria for EXTEND-IA using the RAPID [40] (iSchemaView, RAPID, Menlo Park, Calif., USA) analysis system. Initially, SWIFT-PRIME used similar penumbral inclusion/exclusion criteria; however, this was later revised to allow the use of CT ASPECTS so that sites without access to CTP could take part in the study. In spite of this, 81% of the patients in SWIFT-PRIME underwent CTP and analysis with RAPID. A majority of these patients (84.2%) had a target mismatch indicating a small ischaemic core and significant salvageable ischaemic penumbra [1]. The use of penumbral imaging not only allowed these studies to select for patients most likely to benefit from quality reperfusion but also identified a patient population at lower risk of complications. Both trials achieved very low mortality rates in the interventional group (9.0% combined) and the IV-tPA group (14.4% combined) in spite of the severe stroke population. Furthermore, in both EXTEND-IA and SWIFT-PRIME, no interventional patients had symptomatic intracerebral haemorrhage. While this was not statistically significant in individual trials, combining both sets of data achieves statistical significance (0 vs. 3.8%, $p < 0.05$ unadjusted analysis). This indicates that penumbral imaging selects patients who are not only good candidates for functional independence but also selects patients who can expect very low rates of complications when quality reperfusion is achieved. It is also worth noting that the low rates of symptomatic intracerebral haemorrhage (3.8%) and mortality (14.4%) seen in these 2 trials (combined data) for patients receiving IV-tPA only. Given that this was a severe stroke population (NIHSS 17), it suggests that penumbral imaging is useful even with the low rates of reperfusion achieved by IV-tPA.

The remarkable success of both EXTEND-IA and SWIFT-PRIME would appear to be due to the combination of exceptional rates of quality reperfusion combined with penumbral imaging-based patient selection. These results may not be broadly generalizable to centres without access to advanced neuroimaging or experienced neurointerventionalists. However, this also raises the question of which sites should be providing this service, given the magnitude of the effect achieved in these trials.

THRACE and THERAPY

Trial and Cost Effectiveness Evaluation of Intra-Arterial Thrombectomy in Acute Ischaemic Stroke (THRACE) has been recently completed. The intermediary results presented thus far indicate success for endovascular treatment when used as rescue therapy for patients failing to respond to intravenous alteplase. Details of the trial currently await full publication including the prespecified cost analysis.

Assess the penumbra system in acute stroke (THERAPY) trial has also been presented but it currently awaits publication. As with many of the other trials, THERAPY was prematurely terminated in light of the overwhelming success of the other recent endovascular trials. However, unlike the other published trials, while THERAPY showed a trend towards improved outcomes for the penumbra system, this did not reach statistical significance. In the absence of a peer-reviewed publication, critical analysis is limited; however, from the presented data thus far, this may be secondary to longer than expected procedure times. Undoubtedly, dissecting the muted success of the THERAPY trial will provide as much or more information on the critical aspects of endovascular surgery for ischaemic stroke, and hopefully this data will soon be published.

Looking Forward

Several issues remain unresolved by the existing trials. The utility of these techniques in the elderly patient has not been definitively established. Previous, early work on stent retrievers suggests that elderly patients have at least as much to gain as younger patients, when quality reperfusion is achieved [41]. Furthermore, thorough imaging-based screening is likely to identify patients with large vessel occlusions but with only mild stroke severity. A previous observational study has suggested that endovascular treatment may offer little benefit to these patients [42]. However, it is unclear what impact penumbral imaging would have on patient selection and therefore patient outcomes. Planned subgroup analysis of pooled data from the above endovascular trials will hopefully provide significant further guidance in treatment decisions for both elderly patients and those with a mild stroke syndrome in spite of large vessel occlusion [43].

Providing patient access to sufficiently trained neurointerventionalists in a timely fashion is now one of the most significant challenges in acute stroke management. Al-

though increasing the number of training positions or facilitating the training of other endovascular specialties to operate on stroke patients may seem like an appealing solution, this may not achieve high rates of good functional outcomes. There is evidence throughout the trials that increasing operator experience is associated with higher rates of quality reperfusion, in particular, TICI 3 reperfusion and therefore, better rates of functional independence. For example, SWIFT-PRIME, which had the most stringent experience requirements also achieved the highest rates of TICI 3 reperfusion [1]. This question may also be addressed by post-hoc analysis of the above trials. However, undoubtedly, the need to place acute stroke patients in the hands of well-trained and experienced neurointerventionalists will be an on-going challenge for health care systems.

With the development of highly effective reperfusion therapy, the concept of neuroprotection could gain new utility. Many neuroprotective agents, which have previously disappointed in clinical use [44, 45], may yet prove useful. With rapid reversibility of cerebral ischaemia, cerebral protection agents could potentially preserve the ischaemic penumbra longer and in a greater number of patients, further improving upon the remarkable achievements of these trials.

Conclusion

The irrefutable evidence supporting the use of stent-retrievers in acute ischaemic stroke has resulted in an immediate change in treatment across the world. In the rush to adopt the new standard of care, many clinicians and hospital systems may have failed to identify the critical elements that lead to success. By comparing the details of previous, unsuccessful trials to those of the more recent, successful batch, it is possible to suggest priorities to which resources and effort may be applied. All patients require screening with neuroimaging techniques to identify a large vessel occlusion and the application of more sophisticated penumbral imaging may reduce the risks from haemorrhagic transformation and overall mortality. Achieving quality reperfusion of the ischaemic penumbra is critical to success. While this should be performed in a timely manner, there is some suggestion that reperfusion quality is more important than time. This final point is possibly the most relevant to designing stroke care systems. It suggests that getting the patient to a skilled operator who is able to achieve high rates of TICI 2b/3 reperfusion should be the focus of stroke care systems.

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