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REVIEW

Initial management of acute ischaemic stroke

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Abstract

The management of acute ischaemic stroke has been revolutionised by effective reperfusion therapies including thrombolysis and mechanical thrombectomy. In particular, mechanical thrombectomy has heralded a new era in stroke medicine. There have also been developments to improve clinical outcomes for patients who have had an acute ischaemic stroke but are not eligible for this procedure. This article presents an update on the initial management of acute ischaemic stroke, including reperfusion therapies, periprocedural considerations and ongoing research for potential improvements in the care of these patients.

Key words: Acute ischaemic stroke; Mechanical thrombectomy; Thrombolysis

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Introduction

Stroke is the second leading cause of mortality worldwide, resulting in more than 6 million deaths each year (World Health Organization, 2019). In the UK, stroke is the fourth leading cause of mortality, with two thirds of stroke survivors experiencing permanent disability (Stroke Association, 2018). Recent and continuing advances in stroke care, particularly in pharmacological and mechanical revascularisation, are resulting in increasing numbers of survivors and improved quality of life. Stroke should therefore be considered a treatable pathology more than ever before.

Stroke affects survivors and their families as well as impacting upon the NHS, social care services and the economy. Over 113 000 people suffer a stroke each year in the UK. Between 2025 and 2035, the incidence of stroke in the UK is projected to increase by 60% and the number of stroke survivors will more than double. It is estimated that the cost of stroke to UK society will reach £43 billion per year by 2025 and £75 billion per year by 2035 (King et al, 2020). Effective initial management of acute ischaemic stroke can potentially mitigate its adverse impact on individuals and on society.

The majority of strokes (~85%) are ischaemic in aetiology, with the remainder being haemorrhagic (Stroke Association, 2018). Acute ischaemic stroke is the result of temporary or permanent occlusion of a cerebral artery with consequent ischaemia and ensuing infarction of brain tissue. Following acute ischaemic stroke, irreversible damage to brain tissue within the core of an infarct worsens with time from onset. The penumbra represents tissue surrounding the core that may be salvageable with reperfusion therapies. Mechanical thrombectomy has been transformative as a therapy for a proportion of stroke patients (~15%) with anterior circulation (internal carotid artery and middle cerebral artery) large vessel occlusion (Goyal et al, 2016). Stroke symptoms lasting less than 24 hours are termed a transient ischaemic attack.

Thorough guidelines for acute stroke are available (Royal College of Physicians, 2016; Powers et al, 2019), but in this fast-moving field they can quickly become outdated. This article reviews acute ischaemic stroke with the aim of providing a practical approach to its diagnosis and initial management. A companion article (https://doi.org/10.12968/hmed.2020.0123) reviews the current critical care management and neuro-therapeutic options after an acute ischaemic stroke.

Patient assessment

Rapid and efficient triaging with quick access to reperfusion treatments leads to improved clinical outcomes in acute ischaemic stroke (Meretoja et al, 2012). The face arm speech time (FAST) test is a globally adopted approach to screen for stroke symptoms. Adding balance and eye signs (BE-FAST) has been suggested to be more inclusive for posterior

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circulation symptoms (Aroor et al, 2017). Although there are nearly two dozen individual pre-hospital screening tools, there is significant heterogeneity in both the sensitivity and specificity of these tests. Specific tools to triage patients with large vessel occlusion so that they can reach a thrombectomy centre, potentially bypassing closer non-thrombectomy centres, are in development and require further validation (Fassbender et al, 2020).

Internationally, a number of scales have been developed to allow diagnosis and ongoing evaluation of stroke severity. Some methods of assessment are tailored to a particular context and these include pre-hospital scoring, functional evaluation and outcome assessment. The National Institutes of Health Stroke Scale (NIHSS) score is widely used for initial assessment and grades stroke severity attributing points to level of consciousness, gaze, vision, facial palsy, motor and sensory deficits, ataxia, language and inattention (0: no stroke, 1–4: minor, 5–15: moderate, 16–20: moderate/severe, 21–42: severe). Although the modified Rankin Scale was developed for outcome assessment, it is now widely used to denote functional status before and after acute ischaemic stroke and subsequent interventions. The modified Rankin Scale ranges from 0–6 (0: no symptoms, through increasing levels of disability, to 6: death).

The Helsinki model of stroke care incorporates twelve measures to reduce thrombolysis delays in acute ischaemic stroke and has subsequently been shown to reduce door-to-needle times. Hospital pre-notification, rapid neurological evaluation with subsequent interpretation of computed tomography imaging and delivery of thrombolysis on computed tomography table are key areas that lead to improved door-to-needle times (Meretoja et al, 2012). Pre-hospital intervention and reducing door-to-reperfusion times are a focus of ongoing studies (Fassbender et al, 2020).

Imaging

Imaging modalities that allow diagnosis and evaluation of acute ischaemic stroke include non-contrast computed tomography, computed tomography angiography and computed tomography perfusion, as well as both diffusion and perfusion weighted magnetic resonance imaging. A non-contrast computed tomography scan of the head is the initial imaging of choice and is readily available in many hospitals. Obtaining a non-contrast computed tomography scan of the head as soon as possible after arrival at a stroke centre is recommended (National Institute for Health and Care Excellence, 2019). In acute ischaemic stroke there may be no appreciable computed tomography findings in the early stages, but a computed tomography scan allows identification of haemorrhagic stroke or any pathology that would preclude thrombolysis (eg tumour). Computed tomography angiography allows identification of large vessel occlusion that may be suitable for mechanical thrombectomy, but obtaining a computed tomography angiography should not delay thrombolysis. The Alberta Stroke Programme Early CT Score (ASPECTS) is a 10-point quantitative score used to review early ischaemia in ten regions of middle cerebral artery distribution (Barber et al, 2000). An ASPECTS score of 6 or more indicates a good volume of salvageable brain tissue (Powers et al, 2019). Computed tomography perfusion and perfusion-weighted magnetic resonance imaging allow the identification of patients with acute ischaemic stroke amenable to reperfusion therapies outside of the usual timeframes (Albers et al, 2018; Nogueira et al, 2018). Imaging should always be considered in the context of a holistic clinical evaluation including the timeline of symptoms, the patient's premorbid functional status and the perceived likelihood of a successful outcome as outlined in **Figure 1**.

Treatment

Stroke unit care requires specialist medical, nursing and therapy staff to provide a coordinated approach in caring for all stroke patients. The value of organised stroke unit care cannot be underestimated and should be available to all stroke patients admitted to hospital (Stroke Unit Trialists' Collaboration, 2013). This article now reviews specific aspects of the clinical management of acute ischaemic stroke.

Physiological management

Physiological management has yet to demonstrate significant efficacy in patients who have had an acute ischaemic stroke. Lying patients flat may be beneficial by maintaining and

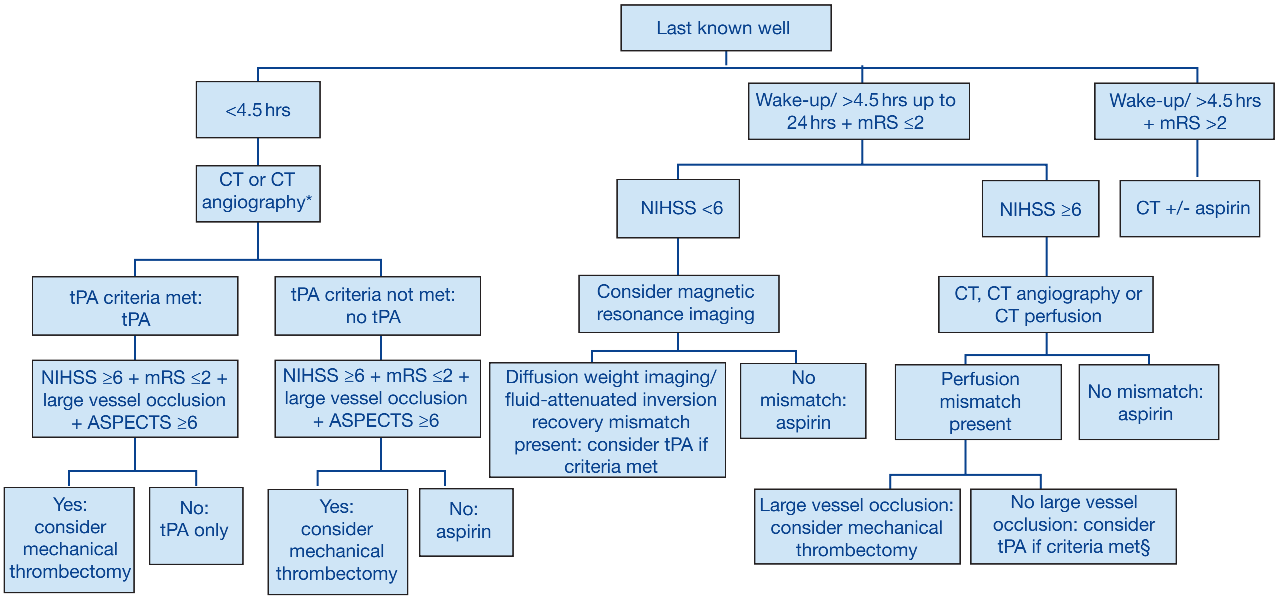

Figure 1. Imaging and management paradigm for acute ischaemic stroke. All stroke patients should receive stroke unit care, and an individualised approach is important, for example frail, dependent people will not be appropriate for advanced imaging or reperfusion therapies. *Computed tomography (CT) angiography should be reserved for patients who are potential thrombectomy candidates, that is modified Rankin scale (mRS) ≤2 and National Institute of Health Stroke Scale (NIHSS) ≥6. §Tissue plasminogen activator (tPA) in wake-up or up to 9 hours since stroke onset. ASPECTS = Alberta Stroke Programme Early CT score.

enhancing cerebral blood flow. A large pragmatic randomised trial (the HeadPoST trial) assessing lying flat vs elevated head positioning found no difference in 90-day functional outcome (Anderson et al, 2017). This trial recruited a population of mild stroke patients and randomised them 14 hours after symptom onset, so its findings cannot be extrapolated to moderate or severe ischaemic stroke patients within the first few hours of onset.

High blood pressure is common in acute stroke and is associated with recurrent ischaemic stroke as well as death and dependency. A reduction of elevated blood pressure to <185/110 mmHg in patients who have had an acute ischaemic stroke and are about to undergo thrombolysis is recommended (Royal College of Physicians, 2016). Intensive lowering of systolic blood pressure to 140 mmHg vs guideline <185 mmHg in the ENCHANTED-BP trial did not influence functional outcome at day 90 (Anderson et al, 2019).

High serum glucose levels within the first 24 hours of acute ischaemic stroke have been associated with poor clinical outcomes but the SHINE trial randomised acute ischaemic stroke patients to either intensive (4.4–7.2 mmol/litre) or standard (4.4–9.9 mmol/litre) glucose control for up to 72 hours, and found no significant difference in functional outcome at 90 days (Johnston et al, 2019).

Hypoxia is common in acute stroke and associated with worse clinical outcomes. However, a large randomised trial assessing prophylactic low-dose oxygen therapy for 3 days in acute stroke found no difference in clinical outcome at 90 days (Roffe et al, 2017). As with the HeadPoST trial, a population of mild stroke patients 20 hours after they were last known well were recruited; therefore, whether oxygen therapy is effective within the initial hours of onset remains unknown. Thus, oxygen therapy is only recommended for acute ischaemic stroke patients with saturations <95% (Royal College of Physicians, 2016).

Antiplatelet therapy

In patients with minor acute ischaemic stroke and high-risk transient ischaemic attack, dual antiplatelet therapy with aspirin and clopidogrel started within 24 hours of symptom onset is effective at reducing recurrent stroke at 90 days (Wang et al, 2013; Johnston et al, 2018). Subsequent meta-analysis revealed an optimum period of 21 days of dual therapy to balance the benefit of preventing further ischaemic events and the risk of bleeding, before switching to ongoing single antiplatelet therapy (Hao et al, 2018). A newer alternative antiplatelet, ticagrelor, has been compared with aspirin within 24 hours of symptom onset in patients with minor acute ischaemic stroke and high-risk transient ischaemic attack and did not reduce recurrent stroke (Johnston et al, 2016). More recently, a large (n=11016) American-led trial found that ticagrelor and aspirin in patients with minor acute ischaemic stroke and high-risk transient ischaemic attack was superior to aspirin alone for preventing stroke or death by 30 days (Johnston et al, 2020). However, it is unclear whether dual antiplatelet therapy with clopidogrel and aspirin is superior to ticagrelor and aspirin with further studies ongoing in this area.

Thrombolysis

Intravenous thrombolysis using alteplase (recombinant tissue plasminogen activator) is widely used for treating patients with acute ischaemic stroke within 4.5 hours of symptom onset (Figure 1) (Royal College of Physicians, 2016). In a meta-analysis of alteplase trials, treatment within 3 hours of stroke onset vs placebo was associated with an increased odds of functional independence at 3–6 months with a number needed to treat of 10 to achieve functional independence in one patient. Treatment with alteplase between 3 and 4.5 hours after stroke onset was also associated with improved functional independence but with a smaller effect size and therefore a number needed to treat of 19 (Emberson et al, 2014). Therefore, the sooner thrombolysis is administered, the better the likely clinical outcome.

Imaging-based selection criteria have led to the treatment of ischaemic stroke patients with alteplase with no clear time of symptom onset or those presenting beyond 4.5 hours (Figure 1). Patients with an acute ischaemic lesion detected with diffusion weighted imaging but not with fluid-attenuated inversion recovery are likely to be within a window for which thrombolysis is safe and effective. The WAKE-UP trial (the efficacy and safety of magnetic resonance imaging-based thrombolysis in wake-up stroke) used diffusion weighted imaging and fluid-attenuated inversion recovery mismatch on magnetic resonance imaging as an entry criterion to then randomise patients to alteplase or placebo (Figure 2). Patients randomised to alteplase had better functional outcome at 90 days compared with those given placebo (Thomalla et al, 2018). Similarly, a meta-analysis of three trials using computed tomography or magnetic resonance imaging perfusion and automated software to detect a target mismatch in those with wake-up stroke or patients presenting up to 9 hours after stroke onset, demonstrated that subsequent randomisation to alteplase is associated with improved clinical outcomes at 90 days compared with placebo. The benefit–risk ratio was larger in patients who met automated perfusion mismatch criteria, ie improved functional outcome and fewer intracranial haemorrhages (Campbell et al, 2019). Therefore, the use of automated software for perfusion imaging is gaining popularity in acute ischaemic stroke.

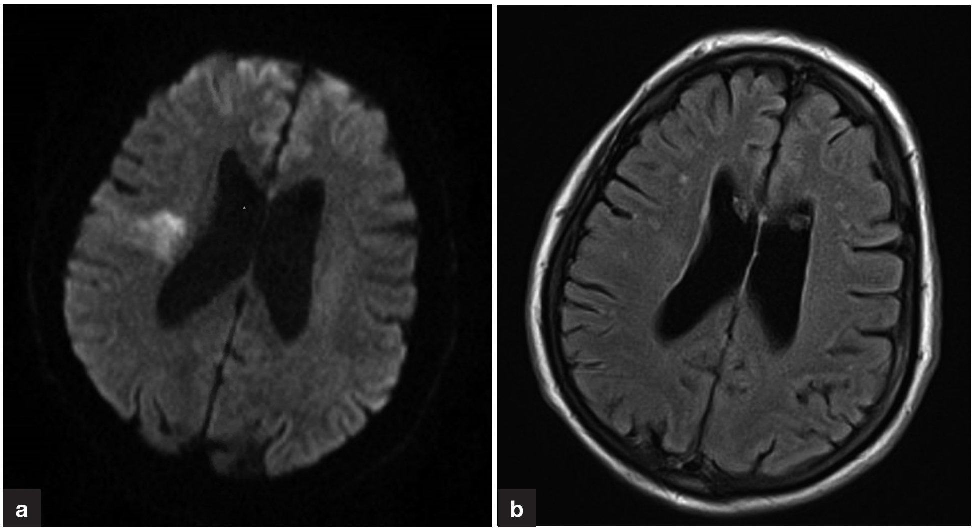

Figure 2. Magnetic resonance imaging diffusion weighted imaging/fluid attenuation inversion recovery mismatch in ischaemic stroke of unknown onset. The patient was last known well at 10:00, found at 15:00, magnetic resonance imaging scan 17:25, thrombolysed at 17:40.
a. Diffusion weighted imaging lesion involving right corona radiata and extending into posterior insula without (b) corresponding fluid attenuation inversion recovery lesion.

The main concern regarding use of alteplase is symptomatic intracranial haemorrhage. The most promising alternative agent is tenecteplase, a tissue plasminogen activator with higher fibrin specificity and a longer half-life than alteplase. In patients with acute coronary syndromes, tenecteplase is widely used with lower rates of systemic bleeding than alteplase. As such, several trials have assessed tenecteplase in acute ischaemic stroke. The large NOR-TEST trial randomised 1100 patients within 4.5 hours of an acute ischaemic stroke to tenecteplase 0.4 mg/kg or alteplase and found no difference in the primary outcome of independent functional outcome at 90 days. Reasons for this result include the substantial number of stroke mimics recruited, which will have diluted any potential treatment effect (Logallo et al, 2017).

In a more targeted trial assessing tenecteplase vs alteplase in those with a large vessel occlusion eligible for thrombectomy (EXTEND-IA TNK), 22% of those randomised to tenecteplase 0.25 mg/kg demonstrated >50% reperfusion of the involved cerebral arterial territory on initial catheter angiography compared with 10% of those randomised to alteplase (P=0.03). EXTEND-IA TNK part 2 demonstrated that tenecteplase 0.25 mg/kg was non-inferior to 0.4 mg/kg in 300 patients with the same inclusion criteria as the original trial (Campbell et al, 2020). The ongoing ATTEST-2 trial seeks to establish the safety and efficacy of tenecteplase 0.25 mg/kg vs alteplase within 4.5 hours of ischaemic stroke onset (NCT02814409).

Mechanical thrombectomy

Mechanical thrombectomy (also termed endovascular therapy), started within 6 hours of stroke onset, has a growing evidence base as the most efficacious therapy for anterior circulation strokes with large vessel occlusion. In these patients, combining mechanical thrombectomy with thrombolysis results in better outcomes than with thrombolysis alone (Goyal et al, 2016). The time at which the patient was last known well is key to decision making for both therapies (**Figure 1**). Mechanical thrombectomy is also indicated where thrombolysis has been unsuccessful or when it is contraindicated.

The aim of mechanical thrombectomy is to recanalise an occluded cerebral artery, to restore normal circulation to the brain and minimise brain tissue damage. Access to the cerebral circulation is usually obtained via the femoral artery. The radial and brachial arteries are alternative access sites and direct common carotid artery puncture is rarely used. Under X-ray control, a guide catheter is advanced to the internal carotid artery, through which a micro-catheter with a guidewire can then be advanced. Removal of the guidewire allows micro-instruments to be passed to the site of arterial occlusion via the micro-catheter (**Figure 3**).

There are several techniques and devices with which clot retrieval can be achieved; these are broadly classified as stent retrievers and aspiration catheters. There is a greater evidence base for the use of stent retrievers (National Institute for Health and Care Excellence, 2018) which are deployed partially within the clot and then removed with the aim of trapping the clot within, to be withdrawn via the micro-catheter. The principle of clot aspiration is to advance the aspiration catheter to the site of occlusion and to then allow aspiration using a pump or manual suction (**Figure 3**). In some cases, both techniques may be used in conjunction to remove the clot.

Figure 3. Thrombectomy angiographic imaging. Terminal left internal carotid artery occlusion on (a) posterior-anterior and (b) lateral views. Aspiration thrombectomy performed with majority of left middle cerebral artery territory recanalised. Small distal branches supplying (c) posterior parietal and (d) occipital territories remain occluded.

Multiple trials have demonstrated the efficacy of mechanical thrombectomy compared with medical therapy (standard care) alone, the mainstay of which has conventionally been thrombolysis with alteplase. The HERMES collaboration conducted a meta-analysis that pooled data from five trials published in 2015 (Goyal et al, 2016). This demonstrated significantly reduced disability at 90 days (measured using the modified Rankin Scale) in patients undergoing mechanical thrombectomy compared with control, with a number needed to treat of 2.6 to improve one patient by one level on the modified Rankin Scale. There was no significant difference in the incidence of parenchymal haematoma, intracranial haemorrhage or mortality between the two groups.

Two trials (DAWN and DEFUSE-3) demonstrated a role for perfusion imaging using either computed tomography or magnetic resonance imaging to identify patients with acute ischaemic stroke in whom treatment may be beneficial outside of the usual therapeutic window for endovascular therapy (<6 hours). The DAWN trial studied the role of mechanical thrombectomy in 206 acute ischaemic stroke patients last known to be well 6–24 hours earlier, where a disproportionately severe clinical deficit compared with infarct size was apparent. Patients were randomised to receive either mechanical thrombectomy plus standard care (n=107) or standard care alone (n=99), with significantly lower disability scores and higher levels of functional independence observed at 90 days in the thrombectomy group (Nogueira et al, 2018).

The DEFUSE-3 trial randomised similar sized cohorts to thrombectomy plus medical therapy vs medical therapy alone, 6–16 hours after stroke onset and showed better functional outcomes with mechanical thrombectomy vs medical therapy alone (Albers et al, 2018). There was no greater risk of mortality, intracranial haemorrhage or serious adverse events in treatment groups in either study. In clinical practice mechanical thrombectomy may be considered for patients with acute ischaemic stroke presenting beyond 6 hours after onset, where ischaemia in the absence of established infarction is demonstrated by perfusion imaging (National Institute for Health and Care Excellence, 2019). Both trials used automated software to process the perfusion imaging to determine eligibility for inclusion.

National registry data from the United States of America suggests that increasing thrombectomy rates are leading to reduced development of malignant middle cerebral artery syndrome and need for decompressive hemicraniectomy (Rumalla et al, 2019).

Anaesthesia for mechanical thrombectomy

Perioperative considerations of relevance for anaesthetists include the need to work expediently, a limited opportunity to glean clinical information, a complex and comorbid patient population, the provision of anaesthesia in the angiography suite (often a remote site) and the maintenance of cerebral perfusion pressure peri-procedurally. In particular, blood pressure should be meticulously managed so as to ensure adequate cerebral perfusion while not increasing the risk of intracerebral haemorrhage and cerebral oedema. A pragmatic approach is to target a systolic blood pressure of 140–180 mmHg (Talke et al, 2014), with appropriate adjustment following recanalisation to prevent haemorrhagic transformation.

There has been continuing discussion as to the optimal anaesthetic technique for mechanical thrombectomy (Dinsmore et al, 2018), with advantages and disadvantages to both general anaesthesia or conscious sedation with local anaesthesia. Three trials have shown that neither technique is superior, with their endpoints as improvement in NIHSS score at 24 hours (SIESTA), modified Rankin Scale score at 90 days (AnStroke) and infarct volume growth (GOLIATH) respectively. These randomised trials were limited by being single centre studies with small sample sizes. Meta-analysis of these three trials found that general anaesthesia was associated with increased functional independence compared with conscious sedation (Zhang et al, 2019). Conversely, a retrospective pooled analysis of the seven trials comprising the HERMES collaboration included 797 patients and showed worse functional outcomes in the general anaesthesia vs non-general anaesthesia subsets when comparing modified Rankin Scale at 90 days (Campbell et al, 2018).

The conduct and nuances of anaesthetic technique including airway management, monitoring, specific drugs, targeted physiological parameters and the interrelation of these factors require further research. The soon to commence European Society of Anaesthesia ARCTIC-I study (Anaesthesia Routine Care for Thrombectomy In Cerebral Ischaemia) is a multicentre observational study which may capture the level of detail required to better define optimal anaesthetic and sedative techniques for mechanical thrombectomy. It seems entirely plausible that there may not be a 'one size fits all' model for anaesthesia and sedation in this context given the heterogenous patient population, varied clinical features and the complex pathophysiology of acute ischaemic stroke. It is therefore reasonable to select an anaesthetic technique for mechanical thrombectomy on an individual patient basis as suggested in the 2019 American Heart Association/American Stroke Association guidelines (Powers et al, 2019).

Future

Key steps in the effective management of acute ischaemic stroke are prompt recognition, early assessment, swift transfer to an appropriate stroke centre and recanalisation of occluded cerebral arteries. Minimising time to reperfusion favourably affects outcomes for both thrombolysis and mechanical thrombectomy.

Mobile stroke units incorporate emergency medical services, a mobile computed tomography scanner and telemedicine, with the aim of initiating therapy for acute ischaemic stroke in the pre-hospital setting. Mobile stroke units allow time delays to be minimised and for an earlier decision to be made for or against thrombolysis, while in transit to a stroke centre. Mobile stroke units are established in several locations globally and much of the associated research has taken place in Germany where the concept originated (Walter et al, 2012). Mobile stroke units shorten the time to initiating therapy from the time of last known well but further research is needed to establish if reduced treatment times result in better clinical outcomes.

The RACECAT study (NCT02795962) aims to establish if patients with acute ischaemic stroke as a result of large vessel occlusion have better outcomes when transferred to local stroke centres or directly to stroke centres with thrombectomy services. This study, being conducted in the Catalan territory in Spain, compares the 'drip and ship' vs 'mothership' models of service delivery.

Conclusions

The initial management of acute ischaemic stroke has dramatically changed in recent years with the advent of thrombolysis and mechanical thrombectomy. Making mechanical thrombectomy available to all potentially eligible patients is an ongoing developing challenge. Improvements in peri-procedural management aim to maximise the benefit of reperfusion therapies. Similarly, newer thrombolytic agents and novel antiplatelet regimens hold promise for the majority of patients who have had an acute ischaemic stroke and are not eligible for thrombectomy.

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Key points

- Rapid identification, assessment and treatment of acute ischaemic stroke is crucial to improve clinical outcomes for patients.
- Thrombectomy for large vessel occlusion in acute ischaemic stroke is a highly efficacious and cost-effective treatment.
- Making thrombectomy services available for all eligible patients is a significant challenge.
- Research seeks to improve the peri-procedural management of patients undergoing thrombectomy.
- Newer thrombolytic agents and antiplatelet regimens seek to improve outcomes for those patients ineligible for thrombectomy.

Conflicts of interest
The authors declare no conflicts of interest.

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