Thrombolytic therapy for stroke

This review article describes thrombolysis as an effective treatment for acute ischemic stroke. The aim of acute thrombolytic therapy is to break up the thrombus or embolus occluding a cerebral artery and restore perfusion to reversibly ischemic brain. Current evidence from randomized, controlled trials limits the therapeutic time window for thrombolysis to 4.5 h for intravenous treatment and 6 h for intra-arterial treatment. Guidelines emphasize the need to identify acute stroke as a clinical priority, and to develop 'fast-track' protocols for the early assessment and treatment of stroke patients. The use of advanced imaging techniques and adjuncts to thrombolysis that may have the potential to improve the ability to select patients who may benefit from reperfusion therapy, and allow treatment decisions to be based on individual brain pathophysiology rather than arbitrary time windows, are discussed.

KEYWORDS: early management ■ imaging ■ reperfusion ■ stroke ■ thrombolysis

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Stroke is a common condition affecting approximately 110,000 people every year in England alone. It is the third leading cause of death and the single largest cause of adult physical disability [1]. A third of individuals who have a stroke are left with a long-term disability that may include weakness, sensory impairment and loss of cognitive and communication skills, depending on the regions of the brain affected. Stroke currently costs the National Health Service and the UK economy GB£7 billion per year – GB£2.8 billion in direct healthcare costs, GB£2.4 billion of informal care costs and GB£1.8 billion in income lost to productivity and disability [1].

Stroke has been defined as a rapid onset of focal neurological deficit with objective evidence of cerebral damage, with no apparent cause other than disruption of blood supply to the brain [2]. This clinical definition includes both hemorrhage and infarction and, although still robust, has been refined by the increasing use of neuroimaging in recent years. Early brain scanning is needed to distinguish other pathology that may mimic stroke, exclude hemorrhage (especially if thrombolysis is being considered) and to provide information on the type and location of stroke, all of which may influence early management decisions [3].

Pathophysiology of ischemic stroke

Ischemic stroke is more common than hemorrhagic stroke, accounting for approximately 85% of cases. The vast majority of ischemic strokes involve athero–thromboembolic processes within the vasculature of the head and neck or embolism directly from the heart. The emboli formed travel through the vascular system, along arteries of decreasing size, until they occlude vessels with a similar diameter. The distal blood supply is then abruptly cut off, preventing delivery of nutrients to the affected area and resulting in ischemic damage. In ischemic stroke, brain tissue receiving little or no blood flow is known as the ischemic core, and is comprised of cells that die rapidly. The ischemic core radiates outward from the occluded area and, typically, 1.9 million neurons are lost for every minute that a stroke goes untreated [1,4]. Surrounding the ischemic core is the ischemic penumbra; tissue that is functionally impaired and at risk of infarction but that may be saved if reperfused. Indeed, the defining principle of acute ischemic stroke therapy is salvaging the ischemic penumbra, and thereby reducing the extent of tissue infarction and improving clinical outcomes [5].

The penumbra contains electrically inexcitable but viable cells, and the duration of ischemia, as well as the absolute flow, plays a crucial role in determining its fate. Experimental studies in primates [6] and cats [7], and clinical studies in humans during carotid endarterectomy [8], have shown that spontaneous and evoked electrical activity ceases when cerebral blood flow falls below 16–18 ml/100 g/min. This level of ischemia therefore represents a threshold for loss of neuronal electrical function (that is, electrical failure). It has been subsequently shown that there is a lower threshold (10–12 ml/100 g/min) for loss of cellular ion

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hemostasis (that is, membrane failure) [9]. At this lower threshold, potassium is released from and calcium is taken up by the cells [10]. Rapid efflux of potassium and uptake of calcium represents a generalized collapse of membrane function, and at this point cells also take up sodium and chloride ions with osmotically obligated water [11]. Penumbral tissue may be considered as that 'hibernating between states of electrical and membrane failure' [5]. The threshold for infarction appears similar to that for energy failure/loss of membrane hemostasis, but it varies with the duration of the insult. For example, in the macaque monkey, tissue with a cerebral blood flow of around 15 ml/100 g/min can withstand approximately 3 h of occlusion, while tissue with a perfusion of around 5 ml/100 g/min will stand only 2 h [12]. This time dependence has crucial significance when considering acute treatment in humans, and implies that treatment will be most successful when it is given as early as possible. Furthermore, the longer that penumbral brain tissue goes untreated, the greater is the chance of it undergoing infarction. Indeed, if perfusion is not restored to the penumbra, any tissue not receiving sufficient collateral arterial supply will undergo infarction (Figure 1). The aim of acute thrombolytic treatment is to break up the occluding thrombus or embolus, restore perfusion to reversibly ischemic brain and reduce the volume of irreversibly damaged brain tissue.

Intravenous thrombolysis: the evidence

Thrombolytic agents are plasminogen activators that catalyze the conversion of the precursor plasminogen to plasmin, which then acts to break down the dense meshwork of cross-linked fibrin strands in blood clots. Studies with the thrombolytic agent streptokinase, which had been successful as a thrombolytic drug in myocardial infarction, were halted prematurely in view of a significant increase in the rate of symptomatic intracranial hemorrhage and no improvement in functional outcome [13–15]. It is not clear if the morbidity and mortality observed with streptokinase in these trials was due to the time interval to treatment (up to 6 h), the dose of drug or the agent itself [16]. Nonetheless, based on these studies, streptokinase is not used clinically to treat acute ischemic stroke.

Recombinant tissue plasminogen activator (rt-PA) was approved for use in acute ischemic stroke in 1996, largely on the basis of the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA study [17]. In this pivotal study, 624 patients presenting within 3 h of symptom onset were randomly assigned treatment with 0.9 mg/kg of intravenous rt-PA or placebo. Whilst neurological improvement did not differ between the two groups after 24 h, clinical outcome was significantly better in the treated group at 3 months. More specifically, the trial showed that, compared with placebo, rt-PA provided a 14% absolute increase in the chance

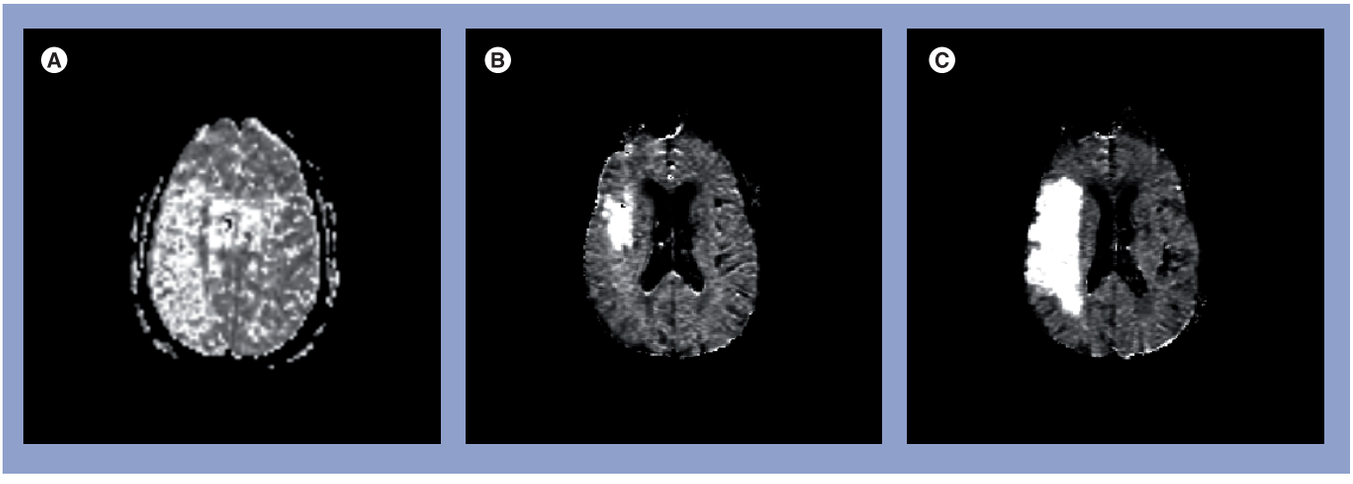

Figure 1. Infarction of the penumbra in acute ischemic stroke. Three brain MRI scans from the same patient with a right middle cerebral artery territory stroke. In the absence of reperfusion, the penumbral tissue, which can be estimated by subtracting the ischemic core in **(B)** from the hypoperfused tissue in **(A)**, undergoes infarction such that almost all of the initially hypoperfused tissue becomes irreversibly damaged. **(A)** Perfusion brain MRI showing hypoperfusion of the right middle cerebral artery territory 12 h after the onset of left-sided hemianopia, neglect, hemiplegia and hemianaesthesia. **(B)** Diffusion-weighted brain MRI showing the ischemic core tissue 12 h after the onset of left-sided hemianopia, neglect, hemiplegia and hemianaesthesia. **(C)** Diffusion-weighted brain MRI showing infarcted tissue 96 h after the onset of left-sided hemianopia, neglect, hemiplegia and hemianaesthesia.

of being alive and independent, and a 13% absolute decrease in the chance of being alive and dependent 3 months after stroke. Symptomatic intracerebral hemorrhage occurred in 6.4% of patients treated with rt-PA, compared with 0.6% of those given placebo [17]. Across the entire spectrum of outcomes, the number needed to treat to cause significant improvement in one patient was estimated to be 3, and number needed to treat to cause harm was 30 [18]. Benefits of treatment with rt-PA were shown to be sustained at 1 year [19] and be cost-effective, particularly by reducing hospital length of stay and institutionalization rate, thus providing a net cost savings to healthcare systems [20]. Furthermore, subsequent analysis of the NINDS trial data demonstrated that the benefit of rt-PA was independent of severity of initial neurologic deficit, age, gender or the presumed stroke subtype. Patients with significant initial neurological deficits, advanced age, thrombus on early brain imaging, diabetes and elevated admission blood pressure did less well than patients without these factors in both the control and the rt-PA-treated groups, but patients with these unfavorable characteristics still had benefit from rt-PA [17,19,21].

Whilst the NINDS study was in progress, other trials began to investigate whether the therapeutic time window for thrombolysis could be increased. Two European Cooperative Acute Stroke Studies (ECASS I [22] and ECASS II [23]) investigated a time window of up to 6 h, while the Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke trial (ATLANTIS) [24] investigated extending the treatment interval for rt-PA by giving 0.9 mg/kg rt-PA within 3–5 h of symptom onset. These trials failed to demonstrate efficacy of thrombolytic treatment, as defined by primary outcomes. However, the ECASS I study had a high percentage of protocol violations (17%) and used a higher dose of rt-PA (1.1 mg/kg) that was associated with higher rates of intracerebral hemorrhage [16]. Also, a *post hoc* analysis of the ECASS II trial (analyzing modified Rankin scores dichotomized for death and dependency), demonstrated a favorable outcome in patients treated with rt-PA (54.3%) compared with placebo (46.3%) (p = 0.024) [23]. A pooled analysis of 2775 patients enrolled in the ATLANTIS, ECASS and NINDS trials showed that the earlier the commencement of thrombolytic therapy, the greater the benefit [25], giving rise to the mantra of 'Time is Brain' (Figure 2) [1]. The pooled analysis, however, also suggested a potential benefit of thrombolysis beyond 3 h.

In September 2008, the results of the ECASS III trial were reported, showing that compared with placebo, rt-PA administered between 3 and 4.5 h after the onset of symptoms significantly improved clinical outcome. This study randomized 821 patients to 0.9 mg/kg of intravenous rt-PA or placebo, and demonstrated 52.4% of patients treated with rt-PA to be alive and independent 3 months after stroke, compared with 45.2% of patients receiving placebo [26]. Mortality was not significantly affected and, as with all previous stroke thrombolysis trials, rates of intracerebral hemorrhage were higher in the rt-PA-treated patients compared with those receiving placebo. The symptomatic hemorrhage rate, however, was 2.4% in patients treated with rt-PA compared with 0.2% of those given placebo. It should be borne in mind that definitions of intracerebral hemorrhage differ between thrombolysis trials. The ECASS III definition of symptomatic intracerebral hemorrhage was any hemorrhage associated with death or neurologic deterioration (as indicated by an increase of at least 4 points on the National Institute of Health Stroke Scale [NIHSS] score). The NINDS definition was a hemorrhage not seen on a previous brain scan associated with any decline in neurologic status or any suspicion of hemorrhage [26].

With the exception of the NINDS trial, which included a small number of individuals over the age of 80 years, trials for acute thrombolysis generally excluded patients older than 80 years. Elderly people have poorer outcomes, but this appears to be due to other comorbid conditions

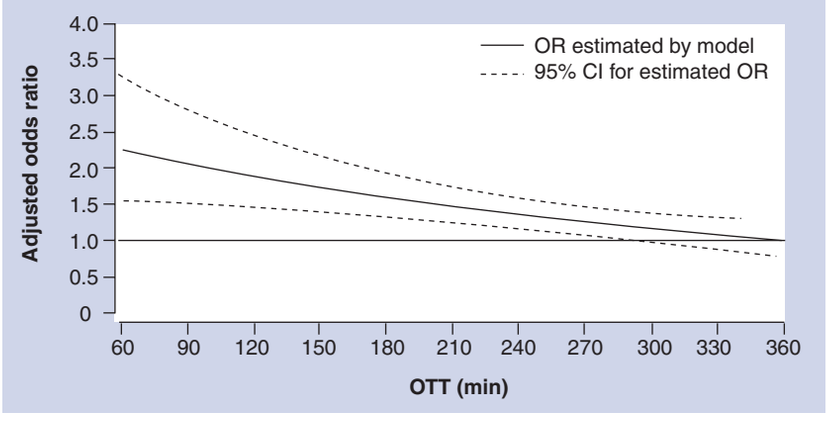

Figure 2. The adjusted odds ratio of a good outcome according to time since stroke onset ('Time is Brain').
OR: Odds ratio; OTT: Onset to treatment time.
Reprinted from *The Lancet*, Hacke W, Donnan G, Fieschi C *et al.*; ATLANTIS Trials Investigators; ECASS Trials Investigators; NINDS rt-PA Study Group Investigators: Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials, 768–774 © 2004 [25], with permission from Elsevier.

rather than age alone, and in observational studies, the rate of symptomatic intracerebral hemorrhage did not differ between patients aged over and under 80 years [27].

Favorable clinical outcome of thrombolysis has been associated with recanalization, and open studies of both carotid and vertebrobasilar territory stroke have demonstrated early and better recovery in patients who had effective reperfusion [22,28–33]. Angiographically controlled studies that predated the NINDS study demonstrated recanalization rates of 40–100% in intraarterial studies, and 34–59% in intravenous studies, with reperfusion being more frequently observed in middle cerebral artery branch occlusion (up to 70%) than in intracranial internal carotid artery occlusion (<10%) [22,28–37]. Poor collateral circulation was shown to be a predictor of poor outcome and development of a space-occupying infarction and secondary hemorrhage [22,38,39]. Indeed, collateral blood flow has been demonstrated to be a significant predictor of functional outcome after thrombolysis [40,41].

Intravenous thrombolysis in practice

After the approval of rt-PA for the treatment of acute ischemic stroke in 1996, observational studies in both North America and Europe confirmed that administration of rt-PA was safe and feasible in a variety of clinical settings, as long as the NINDS guidelines were strictly followed [42–44]. Indeed, rates of symptomatic intracerebral hemorrhage were shown to be lower than those demonstrated in the NINDS trial, even in centers with little experience of thrombolysis [42]. By contrast, when protocols and guidelines were violated, rates of symptomatic hemorrhage rose considerably [44].

In order to ensure timely treatment of acute ischemic stroke with rt-PA, fast-track systems have been advocated [45]. This involves protocols being in place that ensure the rapid response of ambulance staff, emergency department clinicians and stroke specialists. Structured assessment tools, such as the Face Arm Speech Test (FAST) [46] and Recognition of Stroke in the Emergency Room [47], have been demonstrated to be effective in the diagnosis of stroke in the prehospital and emergency department, respectively, and have both been implemented in local and national guidelines [1]. These assessment tools have been shown to be accurate in the diagnosis of stroke when used by a variety of healthcare professionals, facilitating the 'fast-tracking' of stroke patients to specialist stroke care [45,46,48]. Fast-track systems also facilitate the initiation of appropriate investigations within the emergency department. This is especially important for those patients who present within a time-frame for thrombolysis, and involves emergency department staff performing venesection, siting cannulae and organizing brain imaging [45].

After a clinical diagnosis of stroke is made, and brain imaging excludes hemorrhage and other causes of an acute neurologic deficit, the NIHSS is often applied to screen candidates for thrombolytic therapy. The NIHSS is the most commonly used acute stroke clinical assessment tool, and is a 15-item neurologic examination stroke scale that evaluates the effect of acute cerebral infarction on level of consciousness, extraocular movement, visual-field loss, motor strength, ataxia, sensory loss, language, dysarthria and neglect. It provides a quantitative measure of stroke-related neurologic deficit, may serve as a measure of stroke severity, is valid for predicting lesion size, short- and long-term outcome and provides a common language for information exchanges among healthcare providers [49]. Scores may range from a minimum of 0 with no deficit, to a maximum of 42. It is designed to be simple, valid, reliable, take less than 10 min to complete and be administered at the bedside consistently by physicians, nurses and therapists trained in its use.

The most commonly used modality of brain imaging in the acute assessment of stroke patients is CT scanning due to its ease of use and availability. CT in acute stroke is highly sensitive for the detection of intracerebral hemorrhage, which results in immediate, and easily visible, hyperattenuation. In contrast, acute ischemic stroke produces hypoattenuation of brain tissue that becomes more apparent over a number of hours, and the significance of early ischemic changes on baseline brain CT scan has been controversial [50–51]. The ECASS I and ECASS II studies showed that the presence of early ischemic changes occupying more than a third of the middle cerebral artery territory before thrombolysis was accompanied by an increase in the hemorrhagic transformation risk and poor clinical outcome [22,23,52]. Furthermore, the Multicenter rt-PA Stroke Survey Group demonstrated that the symptomatic intracerebral hemorrhage rate was multiplied by more than 4 in 1205 patients treated by intravenous rt-PA within 3 h who had early ischemic changes occupying more than a third of the middle cerebral artery territory [53]. However, studies have suggested that the sensitivity and reproducibility of early ischemic

change detection are poor and may depend on the quality of the CT scanner used and on the experience of the reader [54–55]. Concern about the reliable detection of early ischemic change on CT and of its significance in relation to functional outcome and the risk of symptomatic hemorrhage following thrombolytic therapy led to the development of systematic quantitative measures such as the Alberta Stroke Programme Early CT Score (ASPECTS). ASPECTS is a 10-point scoring system that assesses regional early ischemic change on CT brain scanning and it has been shown to be simple, valid and reliable [56]. Although ASPECTS has been widely used in clinical studies, it is not used routinely in all centers [57–59]. As detailed below, treatment decisions may be improved by information from perfusion imaging in centers that have the capability to perform such studies rapidly.

In addition to radiological exclusion criteria to thrombolytic therapy, a number of other contraindications also exist (**Box 1**) and these must be excluded by clinicians prior to commencing rt-PA treatment. Intracerebral hemorrhage is the most feared complication of rt-PA therapy and these contraindications, listed in the NINDS trial, reduce this iatrogenic hemorrhagic risk. The main predictors of clinically significant intracerebral hemorrhage after thrombolysis have been shown to be age, clinical stroke severity (as assessed by NIHSS), high blood pressure, hyperglycaemia and significant early ischemic changes and leukoaraiosis on brain imaging [60]. More recently, scoring systems to predict the risk of hemorrhage after thrombolysis have been developed [61]. In the absence of contraindications, rt-PA is infused, via a peripheral cannula, over 1 h at a dose of 0.9 mg/kg, with 10% of the total dose being given as a bolus over 2 min. In the immediate period after the commencement of thrombolysis, blood pressure is measured regularly and intravenous hypotensive treatment instituted if the blood pressure exceeds 180/105 mmHg, in order to reduce the risk of hemorrhagic transformation. Patients should be managed on an acute stroke unit, in line with national guidelines, with adherence to multidisciplinary policies [1,62]. Antithrombotic drugs

Box 1. Contraindications to thrombolysis for stroke.

- Symptoms rapidly improving
- History of stroke or head injury in the last 3 months
- Major surgery or trauma in the last 14 days
- History consistent with subarachnoid hemorrhage
- History of previous intracranial hemorrhage
- History of seizure at stroke onset
- Systolic blood pressure consistently > 185 mmHg
- Diastolic blood pressure consistently > 110 mmHg
- History of gastrointestinal or urinary tract hemorrhage within 21 days
- Recent arterial puncture at a noncompressible site
- Recent lumbar puncture
- Heparin treatment within last 2 days and an elevated activated partial thromboplastin time
- Hemoglobin < 10 g/dl
- Platelets < 100 × 10^9/l
- International normalized ratio > 1.7
- Glucose < 2.7 mmol/l

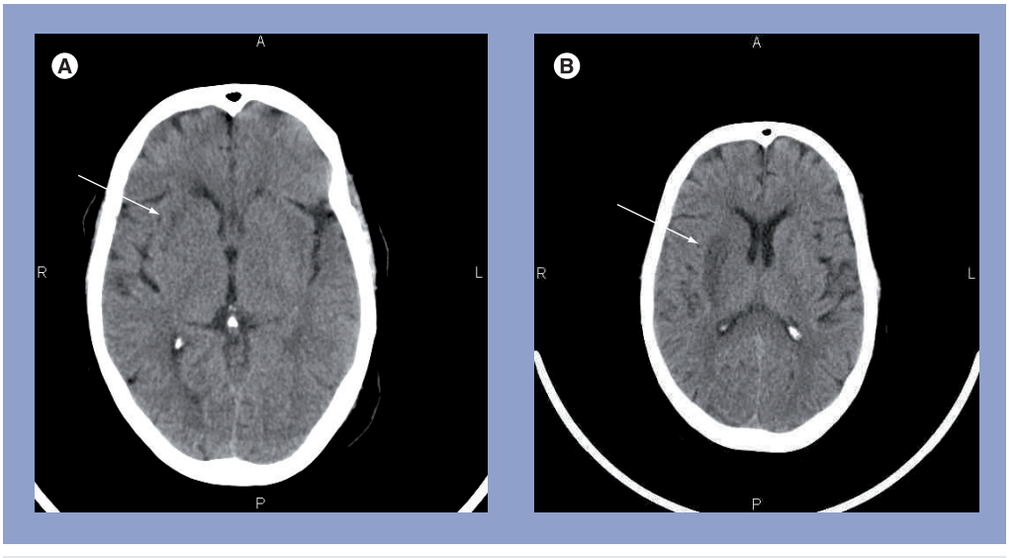

Figure 3. Intravenous thrombolysis for stroke. **(A)** Admission CT brain scan demonstrating minimal early subcortical ischemic change within the right middle cerebral artery territory (arrow) in a 64-year-old man with acute left-sided sensorimotor deficit and inattention (National Institute of Health Stroke Scale [NIHSS] 14). **(B)** Post-thrombolysis scan showing a residual right lentiform nucleus infarct (arrow) but salvage of the rest of the right middle cerebral artery territory. The patient made a good recovery with the only residual deficit being minor left facial paralysis (NIHSS 1).

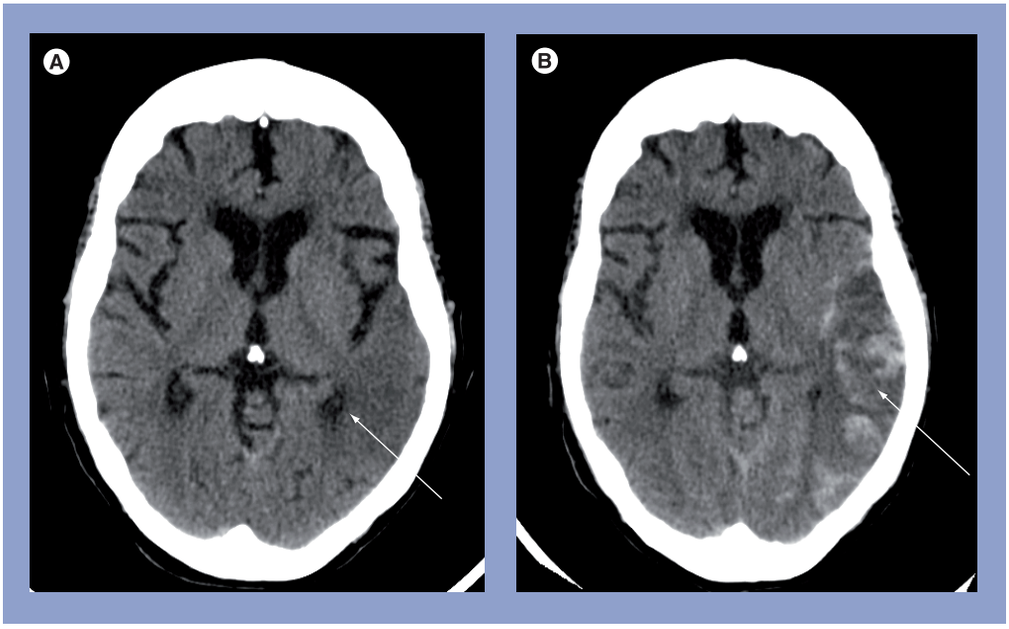

Figure 4. Post-thrombolysis hemorrhagic transformation. **(A)** Admission CT brain scan demonstrating early ischemic change within the posterior third of the left middle cerebral artery territory (arrow) in a 74-year-old woman with an acute onset of aphasia, gaze paresis and right-sided hemianopia, hemineglect, hemiplegia and hemianaesthesia (National Institute of Health Stroke Scale [NIHSS] 25). **(B)** Post-thrombolysis scan showing hemorrhagic transformation of early ischemic tissue (arrow).

are withheld for 24 h until repeat brain imaging to exclude intracerebral hemorrhage and assess for residual structural damage (Figures 3 & 4).

Intra-arterial thrombolysis

Acute ischemic stroke from large vessel intracranial artery occlusion within the internal carotid artery, middle cerebral artery or basilar artery, carries a high mortality if left untreated and has a reduced therapeutic response to intravenous thrombolysis [16]. Indeed, over 80% of patients with an NIHSS of 10 or more have persisting arterial occlusion lesions on subsequent angiography, even after initial treatment with intravenous rt-PA [63]. Theoretically, administering thrombolytic agents directly to the area of clot may increase efficacy and reduce the risk of bleeding, because a high concentration of thrombolytic agents may be delivered into the thrombus [64].

A small randomized, multicenter trial compared intravenous urokinase with intra-arterial urokinase within the first 6 h of acute ischemic stroke, but the study was terminated prematurely because four out of the 14 patients in the intravenous group and three and out 13 in the intra-arterial group died [65]. A further study randomized 16 patients with angiographic evidence of posterior circulation vascular occlusion who presented within 24 h of symptom onset to either intra-arterial prourokinase or conservative management. Some imbalance between groups existed, with greater severity of deficit at baseline observed in the treatment arm. Good outcomes were observed in four of eight patients who received intra-arterial urokinase compared with one of eight patients in the control group, and this led to suggestions that intra-arterial therapy may be used in this setting [66,67].

The Prolyse in Acute Cerebral Thromboembolism Trials (PROACT I and II) investigated the efficacy and safety of intra-arterial thrombolysis for acute middle cerebral artery territory stroke with prourokinase [68,69]. Despite showing no significant difference in 90-day functional outcome or mortality and an increased symptomatic intracerebral hemorrhage rate (15.4 vs 7.1%), PROACT I demonstrated improved recanalization rates (57 vs 0%) in 40 patients with acute ischemic stroke of less than 6 h duration caused by angiographically proven middle cerebral artery occlusion who received 6 mg/kg of intra-arterial prourokinase at the site of occlusion [68]. PROACT II subsequently evaluated the effect of 9 mg of intra-arterial prourokinase in 180 patients with acute ischemic stroke of less than 6 h duration caused by angiographically proven middle cerebral artery occlusion, and whilst there was again no difference in mortality and an increased rate of

symptomatic intracerebral hemorrhage (10 vs 2%) and recanalization (66 vs 18%), outcome measures showed 40% of prourokinase-treated patients to have mild or no disability at 90 days compared with 25% of controls (p = 0.04) [69]. Patients and controls in both PROACT trials also received intravenous heparin infusions.

On the basis of PROACT II, intra-arterial thrombolysis has been recommended as an option for treatment of selected patients who have major stroke of less than 6 h duration owing to occlusion of the middle cerebral artery and who are not otherwise candidates for intravenous rt-PA (FIGURE 5) [67]. This is particularly relevant to patients who have contraindications to the use of intravenous thrombolysis, such as recent surgery. However, clinical benefit may be counterbalanced by delays to initiating treatment with the intra-arterial approach, and treatment requires the patient to be at an experienced stroke center with immediate access to cerebral angiography and qualified interventionalists [67]. The availability of intra-arterial thrombolysis should generally not preclude the intravenous administration of rt-PA in otherwise eligible patients, and time to treatment is just as important in intra-arterial thrombolysis as it is in intravenous thrombolysis [70]. The concept of combining the advantages of intravenous rt-PA (speed of and certainty of initiation of therapy, as well as widespread availability) and intra-arterial recanalization therapy when possible (titrated dosing, mechanical aids to recanalization and possibly superior and earlier recanalization) has been evaluated in pilot trials and advocated as an optimal treatment for patients with angiographically proven large vessel occlusion [63]. Furthermore, pilot studies have demonstrated the feasibility of rescue localized intra-arterial thrombolysis for acute ischemic stroke patients after early nonresponsive intravenous rt-PA therapy [71]. A randomized multicenter trial is currently underway to determine whether a combined intravenous/intra-arterial approach to recanalization is superior to standard intravenous rt-PA alone when initiated within 3 h of acute ischemic stroke onset [72]. In addition, this trial (IMS III) also aims to test the safety, feasibility and potential efficacy of approved catheter devices as part of the combined intravenous/intra-arterial approach to recanalization.

Perfusion imaging

Despite the evidence for thrombolytic treatment for acute ischemic stroke, thrombolysis is utilized in a disappointingly low percentage of patients. It has been reported that less than 1% of patients in the UK actually receive this recommended therapy [1]. In addition to poor public awareness about stroke symptoms and fear of iatrogenic hemorrhage among clinicians, the primary reason for this statistic is the narrow therapeutic time window for thrombolysis.

Salvaging the penumbra is a fundamental concept in the treatment of acute ischemic stroke with thrombolysis. The amount of brain tissue that can be saved progressively diminishes with time, but the exact rate and amount of viable tissue remaining is unknown. It is therefore difficult to know reliably and accurately the ratio of ischemic tissue to infarcted tissue simply

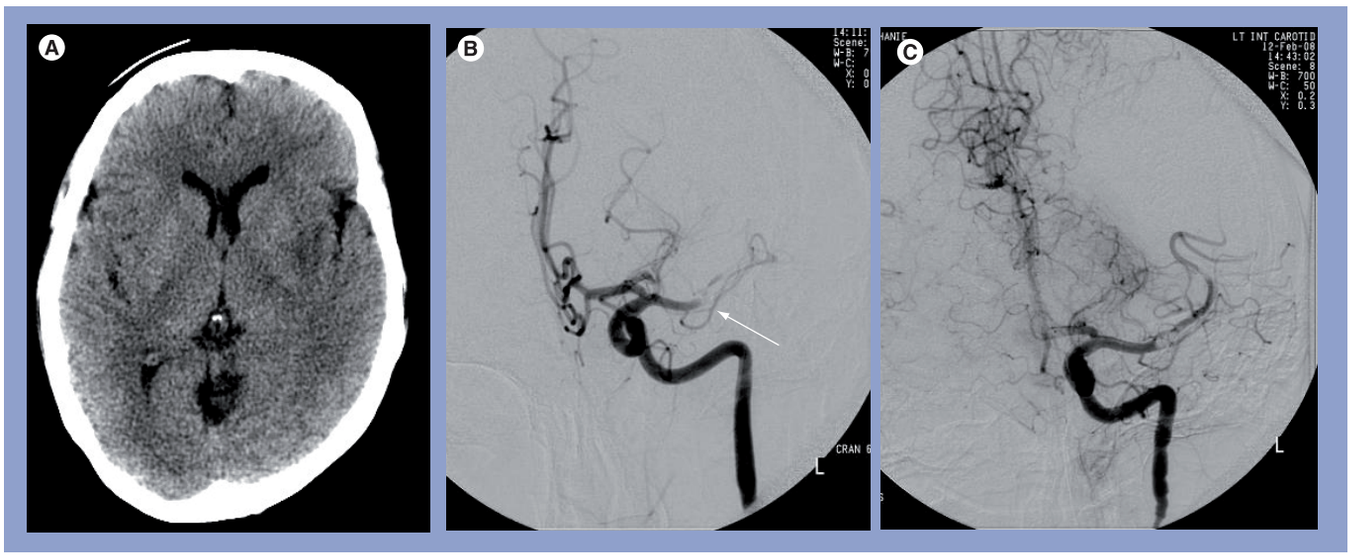

Figure 5. Intra-arterial thrombolysis. **(A)** Admission CT scan showing early infarction of left internal capsule; **(B)** Pre-treatment angiogram (arrow shows location of clot) showing occlusion of the proximal middle cerebral artery; **(C)** Post-treatment angiogram showing successful recanalization after thrombolytic treatment delivered at the site of the clot.

on the basis of time alone. Perfusion imaging allows direct visualization of the brain *in vivo* that enables accurate delineation of potentially salvageable tissue from irreversibly infarcted tissue. This has the potential to improve the ability to select patients who may benefit from reperfusion therapy and allow treatment decisions to be based on individual brain pathophysiology rather than arbitrary time windows (FIGURE 6) [5]. DWI in Evolution For Understanding Stroke Etiology (DEFUSE) and EchoPlanar Imaging THrombolytic Evaluation Trial (EPITHET) are the two largest international multicenter clinical trials that have utilized perfusion imaging in identifying patients with acute ischemic stroke most likely to benefit from reperfusion therapy [73,74]. Both examined thrombolysis in the 3–6 h time window, confirmed that early reperfusion was associated with a more beneficial clinical response in patients with a perfusion mismatch profile compared with those without a mismatch profile, and advocated further Phase III randomized, controlled studies. The Desmoteplase In Acute Stroke (DIAS) I and II and Dose Escalation of Desmoteplase for Acute Ischemic Stroke (DEDAS) randomized, controlled trials have investigated extension of the thrombolytic time window to 9 h with the novel thrombolytic agent desmoteplase [75–77]. Whilst DIAS I and DEDAS initially showed promising results, the larger DIAS II trial subsequently demonstrated no benefit of thrombolysis with desmoteplase in the 3–9 h time window. The authors suggested that a high response rate in the placebo group may have been explained by the mild strokes recorded with low baseline NIHSS scores and small ischemic core lesions, and small mismatch volumes that were associated with no vessel occlusions [77].

Perfusion imaging has also been used to select patients for investigation of other novel thrombolytic agents, such as tenecteplase. Tenecteplase is a modified tissue plasminogen activator with a longer half-life and higher fibrin specificity than rt-PA, and its use in the treatment of ischemic stroke has been investigated in nonrandomized studies [78]. One pilot study has recently compared tenecteplase and rt-PA in patients presenting 3–6 h after the onset of ischemic stroke, with a perfusion lesion at least 20% greater than the infarct core on brain imaging, and demonstrated greater reperfusion (mean 74 vs 44%, p = 0.01), major vessel recanalization (10/15 vs 7/29, p = 0.01) and major neurologic improvement at 24 h (NIHSS reduction ≥8) in patients who received tenecteplase compared with rt-PA [79].

Adjuncts to thrombolysis

Ultrasound-enhanced thrombolysis

In experimental studies, the use of transcranial Doppler ultrasound (TCD) has been shown to increase fibrinolytic activity with putative mechanisms including improved drug transport, reversible alteration of the fibrin structure and increased binding of rt-PA to fibrin [80–82]. The Combined Lysis of Thrombus in Brain ischemia with Transcranial Ultrasound and Systemic TPA (CLOTBUST) I and II trials sought to investigate this *in vivo*. CLOTBUST I was a Phase I nonrandomized, nonblinded trial in stroke patients

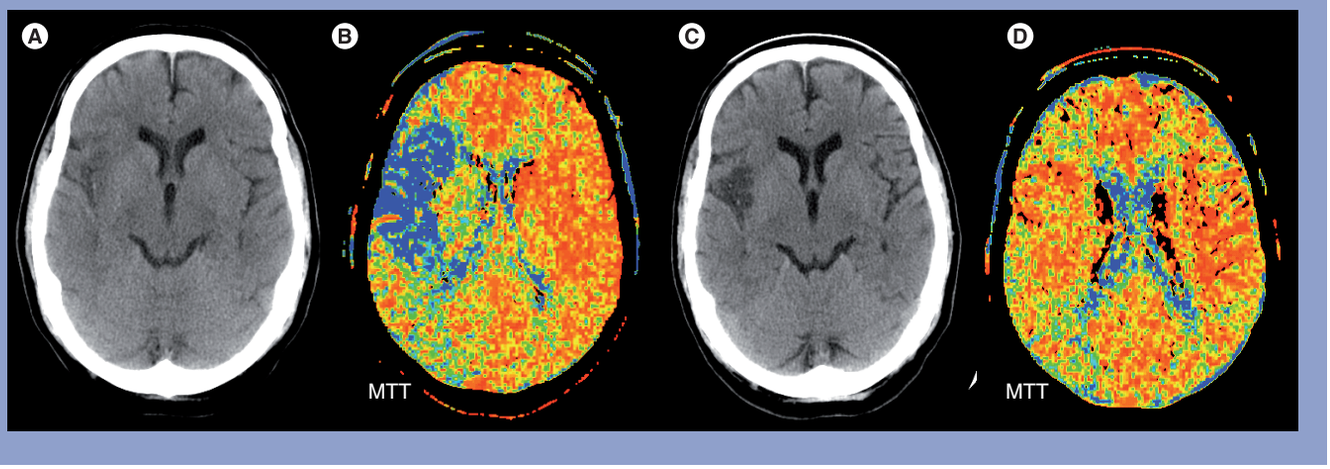

Figure 6. Perfusion CT imaging in acute stroke. **(A)** Admission CT brain scan demonstrating minimal early subcortical ischemic change within the right middle cerebral artery (MCA) territory; **(B)** Perfusion CT scan on admission showing reduced perfusion in the entire MCA territory; **(C)** Plain CT scan 24 h after thrombolysis showing maturation of early changes but no further infarction; **(D)** Perfusion CT scan 24 h after thrombolysis showing restoration of blood flow.
MTT: Mean transit time.

with proximal arterial occlusion receiving intravenous rt-PA within 3 h of symptom onset, who were monitored with portable diagnostic TCD equipment [83]. Complete recanalization (associated with better recovery) on TCD within 2 h after rt-PA bolus was found in 20 of 55 patients (36%) and overall symptomatic hemorrhage rate was 5.5%. The CLOTBUST II trial was a prospective, randomized, multicenter clinical trial studying 126 patients with acute ischemic stroke owing to occlusion of the middle cerebral artery who received intravenous rt-PA within 3 h after the onset of symptoms. Complete recanalization or dramatic clinical recovery within 2 h after the administration of an rt-PA bolus occurred in 49% of the patients assigned to receive continuous 2-MHz TCD, compared with 30% in the control group (p = 0.03). However, outcomes at 24 h and 3 months were not significantly different between groups [84]. Symptomatic intracerebral hemorrhage occurred in three of 63 patients in each of the target and control groups.

Experimental studies have shown that ultrasound-enhanced thrombolysis may be improved by intravenous or intra-arterial administration of microbubbles (small air- or gas-filled microspheres with specific acoustic properties) [85–89]. One clinical trial demonstrated 2-h recanalization rate and 24-h clinical improvement (defined as an increase of >4 points in the NIHSS score) to be greater in patients (n = 38) treated with rt-PA, TCD and microbubbles (55%) compared with rt-PA plus TCD (n = 38, 41%) and rt-PA alone (n = 36, 24%) [90].

Endovascular mechanical thrombolysis

The limitations of intravenous and intra-arterial thrombolysis, as well as the desire to demonstrate improved recanalization rates and long-term outcomes, prompted the development of interventional endovascular strategies that include mechanical thrombectomy with the MERCI device and the Penumbra System™, in addition to intracranial angioplasty and stent placement [91].The MERCI device consists of a flexible tapered wire with five helical loops that can be embedded within the thrombus for retrieval, whilst the Penumbra system is a device by which a thromboembolic clot can be removed from large intracranial vessels via aspiration, mechanical disruption and extraction. Nonrandomized clinical studies have demonstrated both devices to achieve successful recanalization within 8 h of symptom onset in patients with large vessel occlusive acute ischemic stroke [92–94].

Hypothermia

Hypothermia has been shown to be effective in improving outcome in experimental models of brain infarction, and reduction of core body temperature has been shown to be feasible in stroke patients in randomized studies [95,96]. An open pilot study of induced hypothermia by surface cooling subsequent to thrombolysis for acute ischemic stroke demonstrated it to be a safe and feasible option, but in order to prevent shivering, there was a need for general anaesthesia (with mechanical ventilation). Therapeutic hypothermia may be achieved in awake patients via endovascular cooling, and this has also been shown to be feasible in pilot studies of acute stroke patients treated with thrombolysis [97,98].

Conclusion

Acute ischemic stroke is a medical emergency that requires timely and appropriate therapy. Thrombolysis is a highly effective treatment, but patients need to be identified early and selected carefully. This requires the involvement of several professionals in different clinical, laboratory and imaging settings working within strict time restraints, and organization and coordination of various processes is crucial to provision of this treatment. Prudent use of intravenous rt-PA according to established guidelines is effective in improving long-term outcomes and reducing disability in patients presenting within 4.5 h of symptom onset. Intra-arterial thrombolysis is promising up to 6 h after onset, especially in patients with angiographically proven large vessel occlusion. Despite the knowledge that the duration and extent of penumbral tissue varies between patients, the selection criteria for thrombolytic therapy for stroke has historically been determined by time from symptom onset. As technology advances, faster and more accurate visualization of penumbra may change from straightforward anatomic imaging to functional imaging that guides the appropriateness of therapy.

To improve the efficiency of acute stroke thrombolysis in a way that is similar to current treatment of acute coronary syndrome, multimodal combination therapies will need to be developed. Such combination therapy should not only increase the likelihood of favorable outcomes, but should also reduce the likelihood of intracranial hemorrhage. Faster and more complete recanalization should also translate into better patient outcomes. The importance of concomitant excellent general medical care cannot be undervalued, and stroke patients should be

admitted to acute stroke units for the prevention of complications, appropriate assessment, risk factor modification and rehabilitation.

Future perspective

Future practice will be influenced by new studies aimed at increasing the safety of thrombolysis and the therapeutic time window by using MR and CT techniques to assess the ratio of underperfused to damaged brain tissue (the physiological time clock) for thrombolytic decisions. There will be further developments in intravascular procedures, such as intra-arterial thrombolysis, clot retrieval and angioplasty with or without stenting, many of which are being currently investigated. It is also likely that newer and safer thrombolytic agents will become increasingly available. These advances will catalyze the training of highly specialized practitioners to deliver these interventions.

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Executive summary

- Typically, 1.9 million neurons are lost for every minute that a stroke is left untreated.
- Thrombolytic therapy aims to break up the thrombus or embolus occluding a cerebral artery and restore perfusion to reversibly ischemic brain.
- Thrombolysis in selected patients salvages brain tissue at risk and reduces dependency in survivors.
- Early assessment and treatment of stroke patients provides clinical benefit.
- Evidence from randomized controlled trials supports intravenous thrombolysis within 4.5 h of symptom onset and intra-arterial thrombolysis within 6 h of symptom onset.
- The use of advanced imaging techniques and adjuncts to thrombolysis may improve the ability to select patients who may benefit from thrombolytic therapy.

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