

**REVIEW ARTICLE**

# The exact science of stroke thrombolysis and the quiet art of patient selection

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The science of metric-based patient stratification for intravenous thrombolysis, revolutionized by the landmark National Institute of Neurological Disorders and Stroke trial, has transformed acute ischaemic stroke therapy. Recanalization of an occluded artery produces tissue reperfusion that unequivocally improves outcome and function in patients with acute ischaemic stroke. Recanalization can be achieved mainly through intravenous thrombolysis, but other methods such as intra-arterial thrombolysis or mechanical thrombectomy can also be employed. Strict guidelines preclude many patients from being treated by intravenous thrombolysis due to the associated risks. The quiet art of informed patient selection by careful assessment of patient baseline factors and brain imaging could increase the number of eligible patients receiving intravenous thrombolysis. Outside of the existing eligibility criteria, patients may fall into therapeutic 'grey areas' and should be evaluated on a case by case basis. Important factors to consider include time of onset, age, and baseline blood glucose, blood pressure, stroke severity (as measured by National Institutes of Health Stroke Scale) and computer tomography changes (as measured by Alberta Stroke Programme Early Computed Tomography Score). Patients with traditional contraindications such as wake-up stroke, malignancy or dementia may have the potential to receive benefit from intravenous thrombolysis if they have favourable predictors of outcome from both clinical and imaging criteria. A proportion of patients experience complications or do not respond to intravenous thrombolysis. In these patients, other endovascular therapies or a combination of both may be used to provide benefit. Although an evidence-based approach to intravenous thrombolysis for acute ischaemic stroke is pivotal, it is imperative to examine those who might benefit outside of protocol-driven practice.

**Keywords:** acute stroke; multimodal imaging; thrombolytic therapy; interventional therapy; multimodal therapy

**Abbreviations:** AHA/ASA = American Heart Association/American Stroke Association; ASPECTS = Alberta Stroke Programme Early Computer Tomography Score; ESO = European Stroke Organisation; IST = International Stroke Trial; NINDS = National Institute of Neurological Disorders and Stroke; rt-PA = recombinant tissue plasminogen activator; TIBI = thrombolysis in brain ischaemia

## Introduction

*'If you cannot measure it, you cannot improve it.'* Sir William Thomson, 1st Baron Kelvin

Despite initial scepticism about stroke care, the landmark National Institute of Neurological Disorders and Stroke (NINDS) trial (NINDS, 1995) not only revolutionized acute ischaemic stroke treatment, but also reinvigorated enthusiasm in acute ischaemic stroke care and further research. Similarly, recent acute ischaemic stroke trials have shed further rays of hope, past therapeutic nihilism to a point where acute ischaemic stroke is now a treatable medical emergency. The recent third International Stroke Trial (IST-3) (Sandercock *et al.*, 2012) has reignited the debate surrounding the potential benefits of thrombolysis for acute ischaemic stroke patients presenting outside current parameters, specifically the thrombolysis time window and the maximum age of treatable patients.

Acute ischaemic stroke is a heterogeneous disorder with multiple causes and complex mechanisms. However, the major trials have confirmed that regardless of the cause, be it cardioembolic, lacunar or dissection, so long as baseline haemorrhage is ruled out, thrombolysis can be beneficial. It is vitally important that patients are rapidly assessed and imaged, and that a judgement be made as to whether there is viable tissue that will recover after reperfusion. Rapid diagnosis and quick decision-making are essential for treatment decisions in the hyperacute phase, decisions normally made before establishing the pathophysiology of the acute ischaemic stroke. The primary therapeutic goal is rapid restoration of blood flow through recanalization, which can be achieved through thrombolytic therapy or mechanical thrombectomy. The ideal thrombolytic therapy is intravenous recombinant human tissue-type plasminogen activator (rt-PA) administered adherent to the established American Heart Association/American Stroke Association (AHA/ASA) or European Stroke Organisation (ESO) guidelines (ESO, 2008; Jauch *et al.*, 2013). Intra-arterial interventions have proven less successful, although meta-analysis is required to determine if these issues can be resolved with better patient stratification.

The evidence presented in this narrative review is limited to acute ischaemic stroke management. The aim of this review is to identify not only patients that fall within current guidelines for thrombolysis, but to distinguish between those who fall outside established guidelines, in whom thrombolysis is absolutely contraindicated, and those who lie within clinical 'grey areas' who, with good clinical acumen may be judged to nonetheless derive benefit from treatment.

## Examination

History taking and prompt structured assessment are crucial components of effective acute stroke management. The clinician should attempt to identify objective signs (such as eye deviation, either through observation or on subsequent imaging) (Simon *et al.*, 2003) and apply quantitative metrics to rapidly make a correct diagnosis and determine a proper course of action. Key

metrics include time of onset, age, and baseline blood glucose, blood pressure, stroke severity—as measured by National Institute of Health Stroke Scale (NIHSS)—and CT changes, as measured by the Alberta Stroke Programme Early CT Score (ASPECTS).

Time of onset should be established as precisely as possible, either from patient history or eyewitness accounts, taking special notice of sudden onset focal neurological deficits, such as disruptions of regularly scheduled activities like cooking or shopping, or abruptly becoming unable to finish reading a page or watching a television programme, or even, in today's social media-savvy world, acute onset 'dystextia' (garbled text messages) (Ravi *et al.*, 2013).

Neurological deficit can be assessed using the NIHSS, a widely used validated scale, which provides a quantitative assessment of stroke severity and is highly reproducible (Kothari *et al.*, 1995a, b). The NIHSS can also be used to chart stroke progression and response to therapy, as well as being a useful communication tool among the stroke team. It has been used to predict both short and long-term outcome in acute ischaemic stroke patients: patients with a NIHSS >20 have only a 4–16% chance of good outcome at 1 year, increasing to 60–70% in those with a NIHSS <10 (Adams *et al.*, 1999; Kwiatkowski *et al.*, 1999), recently reconfirmed (Kwakkel *et al.*, 2010). However, limitations of the NIHSS include lack of detailed assessment of cranial nerves, and low scores for disabling infarctions involving the brainstem or cerebellum (Kasner, 2006). Other commonly used stroke scales include the European Stroke Scale (Hantson *et al.*, 1994), Canadian Neurological Scale (Cote *et al.*, 1986) and the Scandinavian Stroke Scale (Scandinavian Stroke Study Group, 1985), but we favour the NIHSS because it is the most widely used in clinical trials.

Reduced level of consciousness and coma are difficult to assess using existing neurological deficit scores, and coma was an exclusion criterion in the original intravenous thrombolysis trials, but there may be a role for interventional therapies in established vertebrobasilar artery thrombosis.

## Neuroimaging

The goal of neuroimaging is to help establish the clinical diagnosis as early as possible, as time is of the essence in management of acute stroke. The choice of brain imaging modality lies between CT and MRI (Jauch *et al.*, 2013).

A non-contrast CT can easily distinguish ischaemic from haemorrhagic stroke and may also demonstrate early ischaemic changes or sign of arterial occlusion. The AHA/ASA recommends that either non-contrast CT or MRI be completed within 25 min of arrival at hospital, with interpretation by a skilled physician within a further 20 min (Latchaw *et al.*, 2009; Jauch *et al.*, 2013).

## Multimodal stroke imaging

Multimodal CT and MRI techniques can provide a fast, reliable and comprehensive assessment of the presence and extent of ischaemic injury, perfusion status, vessel occlusion and collateral

flow, and exclude intracranial haemorrhage and other mimics of acute ischaemic stroke, such as neoplasm and infection, through the combination of parenchymal, penumbral, and vascular imaging in a single study (Albers *et al.*, 2006; Hopyan *et al.*, 2010), potentially differentiating the reversible ischaemic penumbra from the irreversible infarct core, and enabling improved selection of patients who will benefit from reperfusion therapies (Schellinger *et al.*, 2003; Albers *et al.*, 2006). Multimodal imaging is also a valuable tool in patients with unknown time of symptom onset or 'wake-up' stroke. Whereas the multimodal CT protocol can be performed in <10 min, multimodal MRI may take 15–30 min (Leiva-Salinas *et al.*, 2011); AHA/ASA guideline time constraints should be kept in mind. It is imperative that stroke physicians are familiar with the advantages and limitations of multimodal CT and MRI imaging techniques (Table 1).

## Neuroimaging scales

Several acute ischaemic stroke neuroimaging scores have been developed to improve detection and guide physicians in making better therapeutic decisions and prognostic predictions. Examples include the one-third middle cerebral artery territory method (hypoattenuation in less than one-third of the middle cerebral artery territory) (von Kummer *et al.*, 1996; Silver *et al.*, 2001), the Boston Acute Stroke Imaging Scale (BASIS) (Torres-Mozqueda *et al.*, 2008) and ASPECTS (Barber *et al.*, 2000) (Fig 1). ASPECTS is a standardized and validated 10-point scoring scale developed to quantify the extent of early ischaemic changes in the middle cerebral artery territory on non-contrast CT (Barber *et al.*, 2000). Similarly, the posterior circulation ASPECTS is a predictive scale for quantifying posterior circulation changes (Puetz *et al.*, 2008b). ASPECTS, in combination with specific clinical markers, has been found to be predictive of response to both intravenous (Coutts *et al.*, 2004a) and intra-arterial therapies (Gupta *et al.*, 2012). ASPECTS has been extended for use with magnetic resonance diffusion-weighted imaging (Kosior *et al.*, 2010), quick symptomatic intracranial haemorrhage risk assessment before thrombolytic therapy (Singer *et al.*, 2009), and for scoring of cerebral blood volume (Aviv *et al.*, 2007). It has also been incorporated into clinical trials such as the Interventional Management of Stroke 3 (IMS III) trial (Broderick *et al.*, 2013) and the Solitaire FR Thrombectomy for Acute Revascularisation (STAR) trial (NCT01327989) (ClinicalTrials.gov).

## Treatment of acute ischaemic stroke

### Pharmacological thrombolysis

Although timely restoration of blood flow is the primary therapeutic goal for patients with acute ischaemic stroke, there is need for careful selection of appropriate patients for thrombolytic therapy. In addition to the various thrombolysis protocols and guidelines, certain key metrics (Box 1) known to be predictive of outcome should help guide clinical judgement, leading to correct

diagnosis, appropriate patient selection, and implementation of maximally beneficial therapeutic interventions.

## Acute ischaemic stroke thrombolysis within the standard guidelines

Intravenous alteplase (the active ingredient being rt-PA) is the only Food and Drug Administration (FDA)-approved thrombolytic agent for the treatment of acute ischaemic stroke. Rt-PA is a fibrin-selective thrombolytic agent that breaks fibrin down into fibrin degradation products, ultimately dissolving the thrombus and resulting in recanalization of the occluded artery (Balami *et al.*, 2013a). Criteria for using rt-PA for thrombolysis are outlined in Table 2. Evidence for the benefit of rt-PA for acute ischaemic stroke treatment in suitable patients is derived from trials including the NINDS (1995) and European Collaborative Acute Stroke Study (ECASS, Hacke *et al.*, 2008) (Fig. 2).

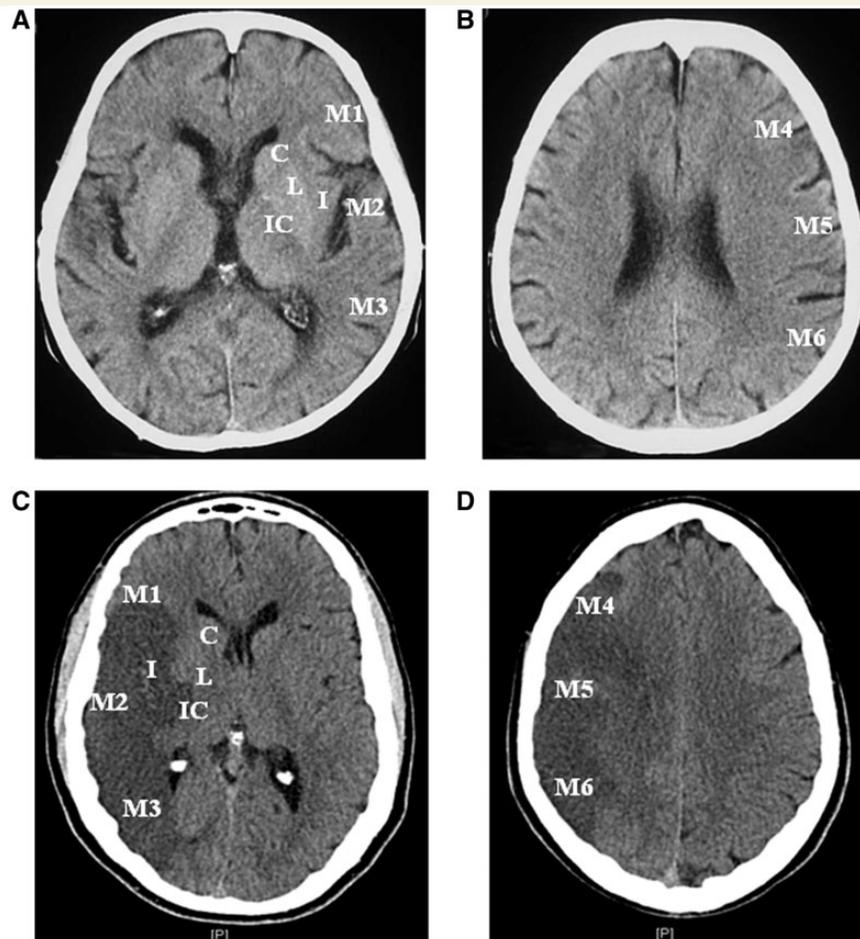
Based on results from ECASS III, in 2009 both the AHA/ASA and ESO guidelines extended the time window for treatment of eligible acute ischaemic stroke patients with intravenous rt-PA from 3 h to 4.5 h after the onset of stroke symptoms (ESO, 2008; Del Zoppo *et al.*, 2009; ESO, 2009), reaffirmed in the recent AHA/ASA guidelines (Jauch *et al.*, 2013). Although the FDA has not yet endorsed use of alteplase beyond 3 h, it has been approved for use up to 4.5 h by the European Medicines Agency. The ECASS III trial of patients given intravenous thrombolysis 3–4.5 h after acute ischaemic stroke onset demonstrated a reduced risk of death or dependency at 3 months (number needed to treat = 14,  $P = 0.04$ ) despite an increase in any intracerebral haemorrhage and symptomatic intracranial haemorrhage (using NINDS definition) (number needed to harm = 10,  $P = 0.001$ ; number needed to harm = 22,  $P = 0.006$ , respectively) (Hacke *et al.*, 2008). The number needed to treat increases from two during the first 90 min (0–1.5 h), to seven during the second 90 min (1.5–3 h), to 14 during the third 90 min (3–4.5 h) after acute ischaemic stroke onset (Hacke *et al.*, 2008). The ECASS III findings are supported by results from the Safe Implementation of Treatments in Stroke-International Stroke Thrombolysis Registry (SITS-ISTR) registry, comparing 664 acute ischaemic stroke patients given intravenous thrombolysis between 3 and 4.5 h with 11 865 patients treated within 3 h (Wahlgren *et al.*, 2008).

A pooled analysis of eight trials showed that intravenous thrombolysis up to 4.5 h from stroke onset can enhance the chance of a favourable outcome. Nonetheless, the analysis showed that the greatest benefit was found in earlier treatment, and that the net benefit diminishes dramatically beyond 4.5 h (Lees *et al.*, 2010). A recently updated systematic review and meta-analysis of 12 trials, including the IST-3, showed that treatment within 6 h of acute ischaemic stroke onset increases patients' chances of being alive and independent by final study follow up [46.3% versus 42.1%, odds ratio (OR) 1.17, 95% confidence interval (CI) 1.06–1.29,  $P = 0.001$ ], although deaths within 7 days were more likely with thrombolysis (8.9% versus 6.4%, OR 1.44, CI 1.18–1.176,  $P = 0.0003$ ) (Wardlaw *et al.*, 2012). However, the greatest benefit is still within the 3 h time window (Fig. 2). Further meta-analysis to

**Table 1 Neuroimaging modalities of acute stroke**

Imaging	Functions	Advantages	Disadvantages
CT			
Non-contrast CT	First line imaging modality for acute ischaemic stroke Information on early signs of ischaemia Exclusion of other stroke mimics	Widely available, cheap, quick, easy to perform and well tolerated.	Provides solely structural not physiological information and cannot reliably differentiate between irreversibly damaged brain tissue from penumbra tissue. Cannot detect petechial haemorrhages
Multimodal CT	Identifies ICH and SAH		Insensitive for detection of small cortical or sub-cortical infarct especially in the posterior fossa CT angiography and CT perfusion may expose patients to additional radiation and intravenous contrast agent.
CT perfusion	Provides information about the penumbra and infarct core	Less time consuming than multimodal MRI	
CT angiogram	Location and extent of arterial occlusion or stenosis and dissection		
CT venogram	Detection of cerebral venous thrombosis		
MRI			
Multimodal MRI		More accurate in demonstrating posterior circulation stroke	Takes longer to perform than CT Not widely available and expensive Contraindicated in patients with pacemakers, defibrillator and metal implants.
DWI	Location, age and extent of acute ischaemia	DWI can detect cortical and subcortical lesions	
PWI	Location and extent of the hypoperfused area		
T <sub>2</sub> -/FLAIR images	Exclusion of other stroke mimics Information on brain parenchyma		
T <sub>2</sub> *-weighted images	Exclusion of intracranial haemorrhages	T <sub>2</sub> *-weighted images can detect small haemosiderin deposits not apparent on CT	
MRA	Location and extent of arterial occlusion/stenosis and dissection		
MRV	Detection of cerebral venous thrombosis		

DWI = diffusion-weighted imaging; ICH = intracerebral haemorrhage; PWI = perfusion-weighted imaging; MRA = magnetic resonance angiography; MRV = magnetic resonance venogram; SAH = subarachnoid haemorrhage.



**Figure 1** Assessing the viability of tissue: the importance of imaging in informed patient selection for thrombolysis. (A and B) ASPECTS = 10 (no changes dictated). (C and D) ASPECTS = 3 (severe tissue damage). Patients with a good scan (A and B) have the potential to respond well to thrombolysis despite a clinically severe stroke. An ASPECTS of >7 predicts a favourable outcome. Patients with a poor scan (ASPECTS <7) (C and D) are less likely to benefit from thrombolysis. C = caudate; L = lentiform; IC = internal capsule; I = insular; M1, M2, M3, M4, M5, M6 = cortical regions.

### Box 1 Quantitative metrics guiding patient selection

- Age
- Time of onset of symptoms
- Baseline:
  - Blood pressure
  - Blood glucose
  - Stroke severity (NIHSS)
  - Early CT changes (ASPECTS)

determine if clinical or imaging scores can serve as independent predictors of outcome is warranted.

Extension of the thrombolysis time window to 4.5 h from acute ischaemic stroke onset creates a new eligible patient population, though it may be marginal in size compared with those presenting within 3 h. A survey of 11 262 patients with acute ischaemic stroke found 14% of <3 h patients, but only 2% of 3–4.5 h patients

eligible for thrombolysis (Mihout *et al.*, 2012). There also remain concerns regarding bleeding risk and low recanalization rates in patients treated in the later time window (Rha and Saver, 2007; Hacke *et al.*, 2008; Lees *et al.*, 2010)—only ~50% of patients achieve recanalization (Rha and Saver, 2007), and even if recanalization is achieved, re-occlusion with neurological deterioration has been reported to occur in >30% (Grotta *et al.*, 2001; Alexandrov and Grotta, 2002; Ribo *et al.*, 2006).

## Acute ischaemic stroke thrombolysis outside the standard guidelines

Evidence for the thrombolysis guidelines comes primarily from the pivotal clinical trials—NINDS, ECASS and ATLANTIS. These trials had several exclusion criteria designed to limit complications associated with intravenous thrombolysis and increase the chance of a positive outcome. Common exclusions include patients presenting outside the recommended time windows and patients with mild or

**Table 2** Guidelines for the use of intravenous alteplase in acute ischaemic stroke

<p><b>Inclusion criteria within guidelines</b></p> <ul style="list-style-type: none"> <li>• Acute ischaemic stroke with a clearly defined time of onset</li> <li>• Likely disabling with no significant improvement or recovery</li> <li>• Treatment initiated within 4.5 h of symptom onset</li> <li>• Age <math>\geq</math> 18 years</li> </ul> <p><b>Absolute contraindications</b></p> <ul style="list-style-type: none"> <li>• Any intracranial haemorrhage</li> <li>• Blood pressure <math>&gt;</math> 185/110 after two attempts to reduce blood pressure</li> <li>• Surgery or trauma within the last 14 days</li> <li>• Active internal bleeding</li> <li>• Haematology abnormalities or coagulopathy</li> <li>• INR <math>&gt;</math> 1.7, APTT <math>&gt;</math> 40, or platelets <math>&lt;</math> 100 000/mm<sup>3</sup></li> <li>• Arterial puncture at a non-compressible site within the last 7 days</li> <li>• Current use of warfarin with INR <math>&gt;</math> 1.7 or PT <math>&gt;</math> 15 s or use of newer oral anticoagulants</li> </ul> <p><b>Modifiable contraindications</b></p> <ul style="list-style-type: none"> <li>• Blood pressure <math>&gt;</math> 185/110 if reduced with antihypertensives after two attempts</li> <li>• Glucose <math>&lt;</math> 2.7 or <math>&gt;</math> 22.2 mmol/l</li> </ul> <p><b>Relative contraindications</b></p> <ul style="list-style-type: none"> <li>• Any of the following IN ISOLATION: hemianopia, neglect, dysarthria, ataxia or sensory symptoms</li> <li>• Pretreatment CT scan showing: <ul style="list-style-type: none"> <li>(1) Hypodensity, which could represent evolving infarction <math>&gt;</math> 4.5 h old</li> <li>(2) Mass effect</li> <li>(3) Oedema</li> </ul> </li> <li>• Tumour, aneurysm, or arteriovenous malformation</li> <li>• Intracranial surgery or intraspinal surgery within the past 2 months</li> <li>• Any non-neurological surgery (including minor surgery) within the past 6 weeks</li> <li>• Stroke or head injury in the preceding 3 months</li> <li>• History of gastrointestinal or urinary tract haemorrhage in previous 21 days</li> <li>• Previous history of CNS bleeding</li> <li>• Endocarditis or acute pericarditis</li> <li>• Recent myocardial infarction within previous 3 months</li> <li>• Serious underlying medical illness, including liver failure, or serious surgical risk (e.g. abdominal aortic aneurysm)</li> <li>• Decreased level of consciousness, not arousable with minimal stimulus (unless likely to be due to basilar occlusion)</li> </ul> <p><b>Potentially treatable (depending on the risk-to-benefit ratio)</b></p> <ul style="list-style-type: none"> <li>• Delayed thrombolysis up to 6 h</li> <li>• Mild stroke/ rapidly improving symptoms</li> <li>• Seizure at stroke onset</li> <li>• Patients on anticoagulation</li> <li>• Patients with dementia</li> <li>• Patients with malignancy</li> <li>• Pregnancy</li> </ul>
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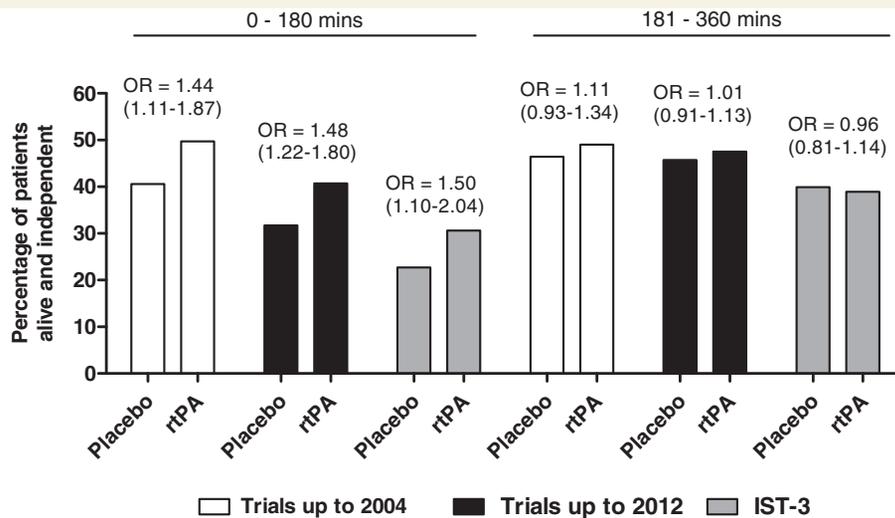
Adapted from the AHA/ASA, 2013.

INR = international normalized ratio; APTT = activated partial thromboplastin time; PT = prothrombin time.

rapidly improving symptoms (Table 2). Limited alternatives to intravenous thrombolysis have persuaded physicians to sometimes offer treatment to acute ischaemic stroke patients with relative contraindications depending on the risk-to-benefit ratio.

### Delayed thrombolysis up to 6 hours

Although benefits of thrombolysis gradually diminish with increasing acute ischaemic stroke onset-to-treatment time, useful clinical benefit remains possible. Multimodal imaging techniques



**Figure 2** Evaluating the importance of time: the effect of rtPA thrombolysis on patient outcome by the end of follow-up. Data were taken from two previously published meta-analyses (ATLANTIS, ECASS and NINDS Investigators, 2004; Wardlaw *et al.*, 2012). Alive and independent, the primary outcome measure, was defined as 0–2 using the modified Rankin Scale or equivalent. Time to treatment was divided between 0–180 min and 181–360 min. A comparison is made between all published trials conducted up to 2004, and all published trials conducted up to 2012. For illustration, IST-3 results were also shown to demonstrate the effects of rtPA in this most recent trial. Unadjusted odds ratios (OR) and their 95% confidence intervals were calculated to compare the effects of rtPA administration with placebo.

(diffusion/perfusion MRI, perfusion CT) may help select patients with salvageable tissue that might benefit from treatment even after 3 or 4.5 h of stroke onset.

The ECASS III trial, which confirmed a clinical benefit within 4.5 h (OR 1.34, CI 1.02–1.76,  $P = 0.04$ ), showed a wider 95% CI (0.9 to 1.5) at 4.5–6 h in the meta-analysis, suggesting the possibility of benefit from intravenous thrombolysis even beyond 4.5 h (Hacke *et al.*, 2008). A meta-analysis of five trials of patients thrombolysed beyond 3 h showed how delayed thrombolysis in patients selected according to mismatch imaging is associated with increased reperfusion/re canalization (Mishra *et al.*, 2010b), but not to improved clinical outcome, and there was a significant risk of symptomatic intracranial haemorrhage and possibly increased mortality. Recently published IST-3 data show that the primary trial hypothesis, that intravenous thrombolysis given within 6 h of acute ischaemic stroke onset increases the proportion of patients alive and independent at 6 months, is not supported on its own, but integrated with other studies in a meta-analysis, a benefit out to 6 h is suggested. An increase in the percentage of thrombolysed patients alive and independent (Oxford Handicap Score 0–2) at 6 months was found to be non-significant (37% versus 35%, OR 1.13, CI 0.95–1.35,  $P = 0.181$ ) (Sandercock *et al.*, 2012). Clinical benefit to 4.5 h has been established, but benefits out to 6 h are equivocal, requiring careful patient selection.

### Thrombolysis for mild acute ischaemic stroke/rapidly improving symptoms

Twenty to forty-six per cent of patients with acute ischaemic stroke with mild or rapidly improving stroke symptoms are excluded from intravenous thrombolysis despite presenting

within the recommended time window (Barber *et al.*, 2001; Katzan *et al.*, 2004; Kleindorfer *et al.*, 2004; Cocho *et al.*, 2005; Schwamm *et al.*, 2005; Majersik *et al.*, 2007; Schumacher *et al.*, 2007; George *et al.*, 2009; Smith *et al.*, 2011). There are several reasons for this exclusion: first is the presumption that prognosis will be good regardless of whether they are given intravenous thrombolysis, more so as potential intravenous thrombolysis risks may outweigh benefits (Adams *et al.*, 2008; Adams, 2009); second is the fact that the NINDS trials excluded acute ischaemic stroke patients with minor symptoms, no measurable deficit on the NIHSS score, symptoms of isolated motor or sensory stroke, isolated ataxia, isolated dysarthria, isolated facial weakness, or rapidly improving deficit (Magid *et al.*, 2005); third, there was no improvement with intravenous thrombolysis among patients with an NIHSS  $\leq 5$  in the NINDS trial (Gladstone *et al.*, 2002); and fourth, many protocols exclude patients who have mild deficits. Consequently, stroke patients with low NIHSS scores are not usually treated in clinical practice, but their outcome is unpredictable, and several may have poor outcomes, as reported in several studies (Nedeltchev *et al.*, 2007; Coutts *et al.*, 2009; Smith *et al.*, 2011). Non-hospital discharge, or disability or death (modified Rankin Score of 2–6), has been reported in 25–64% of acute ischaemic stroke patients with mild stroke or rapidly improving stroke symptoms at hospital discharge (Barber *et al.*, 2001; Smith *et al.*, 2005a; Gonzales *et al.*, 2006; Nedeltchev *et al.*, 2007; Khatri *et al.*, 2008; Coutts *et al.*, 2009), and in 29–58% at 3 months (Khatri *et al.*, 2008; Fischer *et al.*, 2010). In the AHA ‘Get With The Guidelines’ (GWTG) registry of 93 517 patients who presented within 2 h of symptom onset, 29 200 (31.2%) were not eligible for intravenous thrombolysis solely because of mild or improving symptoms, of which 1% died, 28.3% were not

discharged home, and 28.5% were functionally dependent at discharge (Smith *et al.*, 2011). Occasionally, rapid recovery from stroke symptoms is followed by clinical deterioration (Johnston and Easton, 2003; Johnston *et al.*, 2003; Khatri *et al.*, 2012). Persisting large-vessel occlusion, proximal arterial occlusions, and intra- or extracranial carotid stenosis or occlusion substantially increase the risk of early deterioration and are highly predictive of poor functional outcome (Rajajee *et al.*, 2006; Nedeltchev *et al.*, 2007; Coutts *et al.*, 2009).

*Post hoc* analysis of data from the Canadian Alteplase for Stroke Effectiveness Study (CASES) registry suggest that intravenous thrombolysis in patients with baseline NIHSS  $\leq 5$  might be reasonably safe (Steffenhagen *et al.*, 2009). Similarly, the IST-3 showed no significant difference between treated patients with NIHSS  $\leq 5$  compared with those  $> 5$ , although the larger the stroke, the greater the effect of treatment, independent of NIHSS. Although thrombolysis in patients with mild to rapidly improving symptoms remains controversial (Gladstone *et al.*, 2002; NINDS, 2005; Baumann *et al.*, 2006), a subgroup of patients that would benefit from treatment include those with symptoms at presentation perceived to have a disabling deficit despite an NIHSS  $\leq 5$ , taking into account subjective considerations of the functional impact of the neurological deficit on a specific patient's lifestyle. Examples include isolated aphasia or hemianopia, and established proximal arterial occlusions on intracranial vascular imaging, because of the high chance of poor outcomes (Rajajee *et al.*, 2006; Nedeltchev *et al.*, 2007), in addition to patients with small-vessel events who are at risk of significant disability and are more likely to benefit from intravenous thrombolysis (NINDS, 1995, 2005; Khatri *et al.*, 2010). However, further data on reperfusion effects in this subgroup of patients may be warranted.

### Thrombolysis in patients with a seizure at stroke onset

Seizures usually occur early (within 24 h to 2 weeks) after acute ischaemic stroke onset, but can be delayed ( $> 2$  weeks) (Bladin *et al.*, 2000; Lamy *et al.*, 2003; Ryvlin *et al.*, 2006). Occasionally seizures can occur at acute ischaemic stroke onset (Shinton *et al.*, 1988; Selim *et al.*, 2002). Although the reported frequency of early post-acute ischaemic stroke seizures ranges from 2–23%, depending on study design (Burn *et al.*, 1997; Pohlmann-Eden and Bruckmeir, 1997), with late seizure rates of 3–67% (Awada *et al.*, 1999; Camilo and Goldstein, 2004), there are limited data on the frequency of seizures at acute ischaemic stroke onset, although an early study suggested a rate of 5.7% (Shinton *et al.*, 1988).

Seizure at acute ischaemic stroke onset is a relative contraindication for thrombolytic therapy (NINDS, 1995), due to the difficulty in differentiating post-ictal Todd's paralysis from ischaemic stroke paralysis, both clinically and radiologically using non-contrast CT scan (Adams *et al.*, 1996b; Selim *et al.*, 2002). However, multimodal imaging using CT angiography, MRI-diffusion-weighted imaging or perfusion weighted imaging/magnetic resonance angiography can be useful in making the distinction, and may guide thrombolysis decision-making (Schellinger *et al.*, 2000; Sylaja *et al.*, 2006b; Guerrero *et al.*, 2012). The evidence for the safety of thrombolysis in acute ischaemic stroke patients with a seizure at stroke onset has been limited to case series that have suggested that thrombolysis

may be used in the presence of confirmed new ischaemic stroke (Selim *et al.*, 2002; Sylaja *et al.*, 2006b). Both the AHA/ASA and ESO guidelines recommend that patients with seizures at stroke onset be treated with intravenous rt-PA if the neurological deficit is related to acute cerebral ischaemia and not a post-ictal event (ESO, 2008; Jauch *et al.*, 2013).

### Thrombolysis for patients with recent surgery or trauma

The current guidelines contraindicate intravenous thrombolysis in patients having undergone surgery or trauma within the past 14 days, but offer various time windows of relative exclusion, ranging from 21 days to 3 months, for different types of surgery or trauma. No randomized controlled trials have been performed, but case studies suggest that although these patients may benefit from intra-arterial interventions, intravenous thrombolysis remains contraindicated (Katzan *et al.*, 1999; Fukuda *et al.*, 2003; Seifert *et al.*, 2011).

### Thrombolysis for patients on anticoagulation

Controversy surrounds the safety of intravenous thrombolysis in warfarin-treated patients with subtherapeutic international normalized ratio presenting with acute ischaemic stroke (Harrer and Seet, 2012; Miedema *et al.*, 2012). Different centres and regions have variable approaches to the management of such patients. Under AHA/ASA guidelines, patients with acute ischaemic stroke on warfarin are eligible for intravenous thrombolysis if the pretreatment international normalized ratio is  $\leq 1.7$ , whereas in Europe warfarin-treated stroke patients are not eligible (Harrer and Seet, 2012).

A recent review and meta-analysis of seven intravenous thrombolysis studies, in which 6.6% of patients were on warfarin before acute ischaemic stroke onset, found increased symptomatic intracranial haemorrhage risk in the warfarin group (OR 2.6, CI 1.1–5.9,  $P = 0.02$ ), but no significant difference in functional outcome (OR 0.9, CI 0.6–1.2) or death from all causes (OR 1.2, CI 0.9–1.8) (Miedema *et al.*, 2012). Similarly, a retrospective observational study using data from the AHA 'Get With The Guidelines' Stroke Registry found intravenous thrombolysis in the 7.7% of acute ischaemic stroke patients on warfarin (international normalized ratio  $\leq 1.7$ ) was not associated with increased symptomatic intracranial haemorrhage risk (adjusted OR 0.78, CI 0.49–1.24) or in-hospital mortality (adjusted OR 0.94, CI 0.79–1.13), (Xian *et al.*, 2012), suggesting the safety of intravenous thrombolysis in these patients. Further, a prospective observational study found no significant increase in symptomatic intracranial haemorrhage or fatal intracerebral bleed rate in thrombolysed acute ischaemic stroke patients on warfarin (international normalized ratio  $\leq 1.7$ ) (Rizos *et al.*, 2012). There is limited information on thrombolysis in patients taking the newer oral anticoagulants such as dabigatran (Connolly *et al.*, 2009), although a drawback of these drugs is possible difficulty in rapidly reversing their effects.

Further research is required on thrombolysis in this subgroup of patients, although the mortality and functional outcomes in existing studies suggest anticoagulation (with international normalized ratio  $\leq 1.7$ ) should not be an absolute contraindication. Even if they are deemed to fall outside the intravenous thrombolysis recommendations, patients with subtherapeutic anticoagulation could

potentially benefit from rapid stratification to appropriate intra-arterial interventions.

## Thrombolysis in grey areas

Certain conditions present challenges in acute ischaemic stroke patients when thrombolysis is a treatment option, because the risks, benefits and efficacy of thrombolysis are not fully established in conditions such as dementia, despite the guidelines not characterizing these conditions as exclusion criteria. Thrombolysis in such situations therefore remains debatable due to this lack of evidence.

### Thrombolysis for ‘wake-up stroke’ or acute ischaemic stroke of indeterminate onset

Ten to twenty-five per cent of patients wake up with stroke symptoms, or are found unable to communicate the time of stroke onset, the so-called ‘wake-up stroke’ (Nadeau *et al.*, 2005; Mackey *et al.*, 2011), and are not eligible for thrombolytic therapy. However, numerous imaging and clinical studies have suggested that a considerable fraction of wake-up stroke patients may have had acute ischaemic stroke onset just shortly before or after waking up, and may therefore have potentially salvageable penumbral tissue (Fink *et al.*, 2002; Serena *et al.*, 2003; Todo *et al.*, 2006; Adams *et al.*, 2008; Huisa *et al.*, 2010; Silva *et al.*, 2010). Studies have shown no significant differences in baseline clinical characteristics and stroke severity in wake-up stroke relative to stroke-while-awake (Nadeau *et al.*, 2005; Jimenez-Conde *et al.*, 2007). Some studies have found early ischaemic changes on CT in wake-up stroke patients to be similar to those with known time of symptom onset (Serena *et al.*, 2003; Todo *et al.*, 2006). Similarly, prospective analysis comparing wake-up strokes to control acute ischaemic strokes showed similar initial ASPECTS between patients with wake-up strokes and those presenting within 4 h of acute ischaemic stroke onset (Huisa *et al.*, 2010). However, in a subgroup analysis from the Abciximab in Emergency Stroke Treatment Trial-II (AbESTT-II), more new strokes were detected in head CTs of wake-up stroke patients compared to those with known symptom onset within 6 h, although the difference was not significant (Adams *et al.*, 2008). Early analysis of the IST, including 5152 (29.6%) wake-up strokes, comparing presentations and outcomes of wake-up stroke to stroke-while-awake patients, found that wake-up stroke patients might benefit from acute interventions (Moradiya and Janjua, 2012), and a retrospective review of wake-up stroke patients given intravenous thrombolysis (off-label) demonstrated its safety with no increased risk of intracerebral haemorrhage (Barreto *et al.*, 2009).

Penumbral mismatch might be useful for identifying wake-up stroke patients who might benefit from thrombolysis with an acceptable level of risk. A review of the safety and efficacy of MRI-based thrombolysis in unclear-onset stroke comparing patients with unclear-onset stroke and those with clear-onset stroke suggest that intravenous or intra-arterial thrombolysis based on specific MRI criteria may be safely applied to unclear-onset acute ischaemic stroke patients, as rates of recanalization, early neurological improvement, symptomatic intracranial haemorrhage and 3 month outcome did not differ significantly (Cho *et al.*, 2008). The

recently published Tissue Window in Stroke Thrombolysis (TWIST) trial showed how wake-up stroke patients can be safely given intravenous thrombolysis based on a tissue window defined by non-contrast CT and CT angiography/transcranial Doppler, with 34% of wake-up strokes successfully treated, of which 45% had good outcome (modified Rankin Score 0–1). The authors suggested that, given vascular occlusion with a favourable non-contrast CT appearance (minimal early ischaemic changes or high ASPECTS), wake-up stroke patients should be considered for thrombolysis due to the high probability of a salvageable penumbra (Hill *et al.*, 2013). Similarly, a recent observational study in which 56% of wake-up stroke patients were thrombolysed found thrombolysis to be feasible with potential benefit in selected patients based on diffusion weighted imaging–FLAIR mismatch (Manawadu *et al.*, 2013).

Extending the time for Thrombolysis in Emergency Neurological Deficits (EXTEND) is an ongoing trial comparing clinical outcomes of intravenous thrombolysis versus placebo in acute ischaemic stroke patients with significant penumbral mismatch (MRI or CT) from 3–9 h from stroke onset, or wake-up stroke patients within 9 h of midpoint of sleep duration (NCT00887328) (ClinicalTrials.gov). Efficacy and Safety of MRI-based Thrombolysis in Wake-up Stroke (WAKE-UP) is another ongoing multicentre randomized controlled trial of MRI-based thrombolysis in acute ischaemic stroke, aiming to prove the efficacy and safety of MRI-based intravenous thrombolysis in wake-up stroke patients or those with otherwise unknown symptom onset (NCT01525290) (ClinicalTrials.gov), hopefully leading to a larger wake-up stroke evidence base. In light of the existing research, wake-up stroke patients should be assessed for eligibility for thrombolysis if they meet clinical and radiological criteria (i.e. minimal early ischaemic changes, high ASPECTS) in the absence of other contraindications.

### Thrombolysis for patients with dementia

The role of thrombolysis in stroke patients with dementia has remained a grey area, as this condition did not appear in the inclusion or exclusion criteria for major trials. However, most physicians are reluctant to thrombolysise acute ischaemic stroke patients with dementia because of the fear of increased risk of thrombolysis-related intracerebral haemorrhage, due to the higher incidence of silent cerebral microbleeds in the elderly which may be a marker of cerebral small-vessel disease and cerebral amyloid angiopathy, and may therefore increase the risk of intracerebral haemorrhage and poor outcome (Cordonnier *et al.*, 2006; Koennecke, 2006; Henneman *et al.*, 2009). However, a study of patients from CASES found that white matter disease, as diagnosed on CT, although being associated with a higher rate of symptomatic intracranial haemorrhage, did not have an effect on overall clinical outcome at 3 months (Palumbo *et al.*, 2007).

Most physicians are doubtful of the efficacy of rt-PA thrombolysis in older acute ischaemic stroke patients with dementia (Alsheklee *et al.*, 2011). However, a case-control study of intravenous thrombolysis found no significant difference in intracerebral haemorrhage (5.80%) or hospital mortality (17.4%) in acute ischaemic stroke patients with dementia compared to those without (Alsheklee *et al.*, 2011). And in a subgroup analysis of data

from the Registry of the Canadian Stroke Network (RCSN) and Registered Persons Database (RPDB), dementia was not independently associated with mortality, disability, or institutionalization after acute ischaemic stroke. A benefit was suggested in patients with dementia given intravenous thrombolysis, insofar as there were no differences between those with and without dementia in the risk of intracerebral haemorrhage or mortality or disability at discharge (Saposnik *et al.*, 2012b).

In contrast, an analysis of patients  $\geq 80$  years of age who received intravenous thrombolysis or intra-arterial therapy in the 'Get With The Guidelines' database found prestroke dementia to be a powerful independent predictor of in-hospital mortality and poor outcome after acute reperfusion therapy for stroke (OR 3.61, CI 1.39–9.37) (Busl *et al.*, 2011).

With an ageing demographic, an increasing number of elderly patients will present with acute ischaemic stroke and dementia. Further research is needed to fully establish therapeutic protocols, although the studies suggest that at least younger (<80 years old) acute ischaemic stroke patients with dementia may benefit from thrombolysis.

### Thrombolysis in patients with malignancy

There are limited data on the safety of thrombolysis for acute ischaemic stroke in patients with malignancy since this condition was an exclusion criterion from clinical trials (NINDS, 1995) and observational studies (Wahlgren *et al.*, 2007) due to the potential risk of symptomatic intracranial haemorrhage (Hsieh and Chen, 2009).

In a retrospective single centre experience of 308 thrombolysed acute ischaemic stroke patients, 18 (5.8%) had a concurrent malignancy, and 26 (8.4%) had a remote history of malignancy. Concurrent malignancy was not independently associated with increased in-hospital mortality following thrombolysis, as the mortality was attributable largely to medical comorbidities, not to symptomatic intracranial haemorrhage. However, patients with brain metastases were excluded (Masrur *et al.*, 2011). A case series of thrombolysed acute ischaemic stroke patients with cancer, without cerebral metastasis (Casado-Naranjo *et al.*, 2011) reported on the safety of intravenous rt-PA.

Evidence for thrombolysis in acute ischaemic stroke patients with intracranial neoplasm is limited and based mainly on case reports (Grimm and DeAngelis, 2007; Garcia *et al.*, 2009; Hsieh and Chen, 2009; Casado-Naranjo *et al.*, 2011; Neil and Ovbiagele, 2011), including two cases of safe intravenous thrombolysis in acute ischaemic stroke patients with intracranial neoplasm outside of the brain parenchyma without any associated intratumour haemorrhage (Neil and Ovbiagele, 2011).

Further exploration of the risks and benefits of intravenous thrombolysis for acute ischaemic stroke patients with concurrent malignancy is warranted, although case reports suggest that there may be benefit in the absence of intracranial neoplasm.

### Thrombolysis in pregnancy

Acute ischaemic stroke during pregnancy and puerperium is a rare but potentially devastating event, accounting for >12% of all maternal deaths (Simolke *et al.*, 1991; Del Zotto *et al.*, 2011). The reported incidence of pregnancy- or puerperium-associated

acute ischaemic strokes varies considerably, from 4.3–210/100 000 deliveries (Sharshar *et al.*, 1995). Acute ischaemic stroke treatment in pregnancy can be quite challenging due to concerns about potential harm to the foetus, particularly during the first trimester when there is a potentially higher risk of teratogenicity and adverse outcomes in the mother. There are limited data on the safety of thrombolysis in pregnancy because it was an exclusion criterion in clinical trials due to fear of potential maternal and foetal risks, such as placental abruption, premature labour, abortion, retroplacental haemorrhage, peri-partum and postpartum haemorrhage, or even harm to the foetus (Wiese *et al.*, 2006). Data are limited to case reports and small case series. Of the 11 reported cases of thrombolysis in acute ischaemic stroke patients during pregnancy and puerperium, administered from 1–37 weeks gestation (Dapprich and Boessenecker, 2002; Elford *et al.*, 2002; Johnson *et al.*, 2005; Leonhardt *et al.*, 2006; Murugappan *et al.*, 2006; Wiese *et al.*, 2006) and during the postpartum period (Mendez *et al.*, 2008; Ronning *et al.*, 2010), all were associated with improvement in maternal symptoms and delivery of healthy babies, although two were complicated by intracerebral haemorrhage after thrombolysis (Dapprich and Boessenecker, 2002; Elford *et al.*, 2002), an incidence similar to that in non-pregnant patients.

Intra-arterial therapy may be an effective alternative to intravenous thrombolysis to potentially reduce the risk of abruption. There are reported cases of intra-arterial therapy for acute ischaemic stroke in pregnancy (Elford *et al.*, 2002; Johnson *et al.*, 2005) and in the puerperium (Ronning *et al.*, 2010). Admittedly, the number of reported cases is too small to draw any definitive conclusions, but case reports suggest thrombolysis may be feasible and beneficial in pregnancy. Although alteplase does not cross the placental barrier and there is no evidence of teratogenicity from animal studies, potential adverse foetal effects remain unknown (Kojima *et al.*, 1988; Tanaka *et al.*, 1988; Leonhardt *et al.*, 2006). However, in standard obstetric practice, the health of the mother does take precedence over the health of the foetus. Further study on the safety and efficacy of rt-PA thrombolysis in pregnancy is needed, but, in the absence of definitive evidence, benefits and risks of thrombolysis in pregnant acute ischaemic stroke patients should be carefully balanced on a patient-by-patient basis.

## Thrombolysis at extremes of age

### Thrombolysis in older people

About 30% of all acute strokes occur in subjects over 80 years of age (Bonita *et al.*, 1994; Di Carlo *et al.*, 2003; Marini *et al.*, 2004; Sylaja *et al.*, 2006a; Saposnik *et al.*, 2009), yet there are limited trial data in the very elderly (>80 years old), as trials demonstrating the benefit of intravenous thrombolysis have either excluded them or randomized very few (NINDS, 1995; Hacke *et al.*, 2008). Nonetheless, thrombolysis has been shown to significantly decrease the risk of mortality following acute ischaemic stroke irrespective of age (Caso *et al.*, 2007; Mateen *et al.*, 2009, 2010). Unfortunately, patients  $\geq 80$  years old are often excluded from intravenous thrombolysis in clinical practice (Barber *et al.*, 2001;

Hacke *et al.*, 2008; Mishra *et al.*, 2010b), primarily because of fears that older people may be predisposed to a greater risk of intracerebral haemorrhage (Zeevi *et al.*, 2007) due to factors such as impaired rt-PA clearance, increased rates of cardio-embolic stroke, and possible amyloid angiopathy (Simon *et al.*, 2004), in addition to the concern that advancing age is associated with poorer prognosis in terms of increased in-hospital mortality risk (Hacke *et al.*, 2004; Heuschmann *et al.*, 2004; Bateman *et al.*, 2006). However, meta-analyses of thrombolysed patients (Engelter *et al.*, 2006; Pundik *et al.*, 2008; Ford *et al.*, 2010; Mishra *et al.*, 2010b; Costello *et al.*, 2012) did not find increased symptomatic intracranial haemorrhage risk among elderly patients despite their generally less favourable outcomes (Engelter *et al.*, 2006; Ringleb *et al.*, 2007), which were attributable to comorbidities rather than consequences of thrombolysis-related complications (NINDS, 1997b; Derex and Nighoghossian, 2009; Alshekhlee *et al.*, 2010; Fonarow *et al.*, 2010).

A controlled study of the influence of age on thrombolysis outcome in acute ischaemic stroke patients from the Virtual International Stroke Trials Archive (VISTA) study, which analysed patients  $\leq 80$  and  $\geq 81$  years separately, demonstrated the benefit of thrombolysis in the very elderly (Mishra *et al.*, 2010b). Functional outcome, measured by modified Rankin Score, was better in the thrombolysed group (OR 1.39, CI 1.26–1.54,  $P < 0.0001$ ), regardless of whether they were young (OR 1.42, CI 1.26–1.59,  $P < 0.0001$ ) or elderly (OR 1.34, CI 1.05–1.70,  $P = 0.002$ ). Similarly, comparison data from SITS-ISTR and VISTA showed increasing age is generally associated with poorer outcome, but the significant association between treatment and improved outcome at 3 months is maintained even in the very elderly (Mishra *et al.*, 2010a). Also, in the recently published IST-3, where 53% of 3035 acute ischaemic stroke patients were  $> 80$  years old, the adjusted effect of treatment between patients  $> 80$  and  $< 80$  years demonstrated a significant difference ( $P = 0.027$ ), indicative of a larger benefit in the older age group, adding substantially to the meta-analysis demonstrating that the benefits of thrombolysis are at least as large in the elderly as in younger patients (Wardlaw *et al.*, 2012).

The available evidence suggests thrombolysis should not be withheld on the basis of advanced age alone. However, recombinant human tissue-type plasminogen activator randomized controlled trials with no upper age limit, which may better determine efficacy in reducing disability and mortality in older stroke patients, are still needed, because the IST-3 subgroup analysis is based on a non-significant treatment effect in their primary outcome: proportion of patients alive and independent at 6 months when treated within a 6 h time window.

### Thrombolysis in children

Thrombolysis in children is not a well-established practice due to a paucity of safety and efficacy data. Risk of bleeding may be higher, especially in neonates in whom plasminogen concentrations are frequently low, in addition to immature haemostatic and fibrinolytic mechanisms as well as a changing cerebral vasculature (Adams *et al.*, 1996a). In the only large multicentre observational study, involving 687 children with acute ischaemic stroke, only 15 (2%) were thrombolysed, nine intravenous and

six intra-arterial. Four (two intravenous and two intra-arterial) had asymptomatic haemorrhages. Neurological deficit was not defined using any validated scale (Amli-Lefond *et al.*, 2009). This suggests a need for randomized controlled trials in children, although the infrequency of acute ischaemic stroke at this age will make finding a suitably large patient group difficult.

## Pre-thrombolysis management

Management of physiological variables such as blood pressure, blood glucose and body temperature before thrombolysis is crucial as these variables can affect the clinical outcome of acute ischaemic stroke patients treated with intravenous rt-PA.

### Blood pressure

Elevated pretreatment blood pressure is independently associated with an increased likelihood of symptomatic intracranial haemorrhage (Tsvigoulis *et al.*, 2010). Retrospective analysis of the SITS-ISTR demonstrated a strong linear association between systolic blood pressure and risk of symptomatic intracranial haemorrhage (Ahmed *et al.*, 2009). Although the management of blood pressure in the setting of acute ischaemic stroke is controversial, it is recommended that thrombolytic agents should only be administered to patients with systolic blood pressure  $< 185$  mmHg and diastolic blood pressure  $< 110$  mmHg at the time of treatment to avoid haemorrhagic transformation (Adams *et al.*, 2007) or high rates of persisting occlusion and partial recanalization (Tsvigoulis *et al.*, 2007). An observational study suggests that pretreatment of blood pressure in acute ischaemic stroke patients before intravenous rt-PA is not associated with increased rate of haemorrhage or poor functional outcome (Martin-Schild *et al.*, 2008). Elevated blood pressure can be treated with intravenous agents such as labetalol, which is preferred because it is easily titrated and has minimal vasodilatory effects on cerebral blood vessels. Other agents to consider include intravenous nicardipine and transdermal nitroglycerine. If blood pressure does not respond and remains  $> 185/110$  mmHg, rt-PA should not be administered. Use of further aggressive measures in patients with blood pressure  $> 185/110$  mmHg is not recommended because further appropriate control of blood pressure for 24 h may not be possible (Jauch *et al.*, 2013). However, post-thrombolysis, aggressive measures are appropriate to control blood pressure during and for 24 h following therapy.

Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED) is a Phase 3 randomized controlled trial designed to establish the effects of low-dose rt-PA and early intensive blood pressure lowering in acute ischaemic stroke patients, with an estimated completion date of December 2016. ENCHANTED aims to compare the efficacy (clinical outcomes) and safety (symptomatic intracranial haemorrhage rates) of standard dose (0.9 mg/kg) versus lower dose (0.6 mg/kg) intravenous thrombolysis, in addition to comparing the efficacy and safety of current blood pressure control recommendations ( $< 185$  mmHg systolic blood pressure) to rapid intensive blood pressure lowering (to below 150 mmHg systolic blood pressure) (NCT01422616) (ClinicalTrials.gov).

## Blood glucose

Hyperglycaemia is one of the most important predictors of poor outcome in acute ischaemic stroke patients, with or without intravenous thrombolysis. Hyperglycaemia  $>7.7$  mmol/l before thrombolysis has been shown to be an independent risk factor for recanalization failure (Ribo *et al.*, 2005), and has been associated with diminished neurological improvement, greater infarct size, and worse clinical outcome at 3 months after treatment (Alvarez-Sabin *et al.*, 2003). In a cohort of thrombolysed acute ischaemic stroke patients from CASES, admission glucose  $>8.0$  mmol/l was independently associated with increased risk of death (adjusted relative risk 1.5, CI 1.2–1.9), symptomatic intracranial haemorrhage (adjusted relative risk 1.69, CI 0.95–3.00), and poor functional outcome at 3 months (adjusted relative risk 0.7, CI 0.5–0.9) (Poppe *et al.*, 2009). Similarly, in the SITS-ISTR registry of intravenous-treated patients, blood glucose  $>6.6$  mmol/l was associated with significantly higher odds for mortality (OR 1.24, CI 1.07–1.44,  $P = 0.004$ ) and lower odds for independence (OR 0.58, CI 0.48–0.70,  $P < 0.001$ ), and blood glucose of 10–11 mmol/l was associated with increased risk of symptomatic intracranial haemorrhage (OR 2.86, CI, 1.69–4.83,  $P < 0.001$ ) (Ahmed *et al.*, 2010). These findings suggest that ultra early glycaemic control pre-intravenous thrombolysis may improve outcomes, and correction with rapidly acting insulin is recommended in most published guidelines (ESO guidelines: to  $<10$  mmol/l; AHA/ASA guidelines: maintain within 7.7–9.9 mmol/l).

The Stroke Hyperglycemia Insulin Network Effort (SHINE) trial is an ongoing multicentre randomized controlled trial of 1400 patients, with results expected in 2018, hypothesizing that treatment of hyperglycaemic acute ischaemic stroke patients to a targeted glucose concentration (4.4–7.15 mmol/l) will be safe and result in improved 3 month outcomes (NCT01369069) (ClinicalTrials.gov).

## Post-thrombolysis management

Following intravenous thrombolysis it is crucial that thrombolized patients, even those with clinical improvement, are closely monitored for possible neurological deterioration. Patients must be admitted to a hyper-acute stroke unit for the first 24 h post-intravenous thrombolysis for strict haemodynamic and neurological monitoring. The concept of specialized stroke units is generally agreed upon as one of the most effective interventions reducing mortality and morbidity after acute ischaemic stroke (Stroke Unit Trialists' Collaboration, 1997, 2007; Saposnik *et al.*, 2008, 2009). One needs close observation and frequent monitoring of patients for early neurological worsening and any signs of symptomatic intracranial haemorrhage or adverse drug reaction. Patients may experience early neurological deterioration, even after initial improvement following intravenous thrombolysis (Saqqur *et al.*, 2007a; Awadh *et al.*, 2010; Delgado *et al.*, 2010), the main causes including haemorrhagic transformation (Berger *et al.*, 2001; Warach and Latour, 2004), cerebral oedema (The Helsinki Stroke Thrombolysis Registry Group, 2012), early recurrent ischaemic stroke (Georgiadis *et al.*, 2006; Awadh *et al.*, 2010), persistent arterial occlusion, partial recanalization, and arterial re-occlusion

(Alexandrov *et al.*, 2000; Christou *et al.*, 2000; Grotta *et al.*, 2001; Saqqur *et al.*, 2007a).

Neurological status (using NIHSS) and blood pressure should be monitored every 15 min for the first 2 h, then every 30 min for 6 h, then hourly for 16 h (Adams *et al.*, 2007). Blood pressure monitoring is recommended for early detection of hypotension, most likely due to overtreatment, which can worsen cerebral ischaemia. Patients should also be monitored for hemi-oro-lingual angioedema, particularly those with pre-existing hypertension who are taking angiotensin-converting enzyme inhibitors (Hill *et al.*, 2003a). This is in addition to monitoring other vital signs such as glucose and oxygen saturation. Data analysis from the Helsinki stroke registry found hyperglycaemia ( $\geq 8.0$  mmol/l) during the 48 h after thrombolysis independently predicted unfavourable outcome, symptomatic intracranial haemorrhage and death (Putala *et al.*, 2011), and a prospective study of 80 thrombolized acute ischaemic stroke patients found blood pressure variability was associated with greater diffusion-weighted imaging lesion growth and worse clinical course (Delgado-Mederos *et al.*, 2008).

A follow-up CT or MRI should be obtained at 24 h to exclude haemorrhage before antiplatelets or anticoagulants are commenced. If haemorrhage occurs, particularly symptomatic intracranial haemorrhage, consultation with neurosurgical specialists and administration of blood products, including fresh-frozen plasma and platelets, should be considered. Similarly, persistence of hyperdense middle cerebral artery sign (HMCAS) on the follow-up CT can be a useful early predictor of poor functional outcome (Paliwal *et al.*, 2012) and may suggest the need for aggressive medical or surgical intervention, such as pre-emptive decompressive craniotomy.

It is also crucial to establish the aetiological factors contributing to the acute ischaemic stroke, such as hypertension, carotid artery stenosis, or atrial fibrillation, and to take appropriate long-term preventative measures (e.g. antihypertensives, carotid endarterectomy, anticoagulation, antiplatelet drugs) to avoid stroke recurrence.

## Predictors of clinical outcome in intravenous rt-PA-treated patients

Factors predicting functional outcome after treatment with intravenous rt-PA include baseline NIHSS, age, admission blood glucose, the presence of hyperdense middle cerebral artery sign, and early ischaemic changes on admission head CT or an ASPECTS  $<7$  (Barber *et al.*, 2000; Coutts *et al.*, 2003, 2004b; Kharitonova *et al.*, 2009; Lees *et al.*, 2010).

## Clinical scoring tools for predicting outcome

Several scoring tools using both clinical and imaging parameters available before initiating thrombolysis have been developed to predict clinical response and long-term outcome in acute ischaemic stroke patients. Examples include the DRAGON score, iScore and hemorrhage after thrombolysis (HAT) score (Lou *et al.*, 2008; Strbian *et al.*, 2011; Saposnik *et al.*, 2012a) (Box 2).

## Imaging scoring tools for predicting outcome

A patient with ASPECTS  $\leq 7$  has been shown to have a 14-fold increased risk of symptomatic intracranial haemorrhage compared to ASPECTS  $> 7$  (Barber *et al.*, 2000). The presence of a hyperdense middle cerebral artery sign and a hyperdense basilar artery sign are associated with less favourable outcomes (Tomsick *et al.*, 1996; Derex *et al.*, 2005; Goldmakher *et al.*, 2009; Nagel *et al.*, 2009), and the hyperdense middle cerebral artery sign on baseline scan may identify patients who require more aggressive therapeutic interventions (Doerfler *et al.*, 1996; Schwab *et al.*, 1998; Manno *et al.*, 2003). Its presence should prompt admission to an ICU or other supervised area. Similarly, hyperdense basilar artery sign can be useful both diagnostically, predicting the presence of basilar artery thrombosis, and prognostically, predicting short- and long-term outcomes in patients with a clinical picture suggestive of posterior circulation infarct (Goldmakher *et al.*, 2009). The presence of hyperdense basilar artery sign will indicate the need for urgent CT angiography and possible transfer to a facility with interventional stroke treatment.

## Complications of intravenous thrombolytic therapy

The majority of complications of intravenous thrombolytic therapy, such as bleeding (intracerebral haemorrhage and systemic bleeding), angioedema and reperfusion injury with oedema, are due to the thrombolytic actions of rt-PA. Others, such as reocclusion and secondary embolization, are related to ineffective thrombolysis or redistribution of the lysed clot. Also, rt-PA can act upon the brain parenchyma, leading to neurotoxicity and seizures (Balami *et al.*, 2013b).

Symptomatic intracranial haemorrhage is one of the most unfavourable and feared complications of intravenous thrombolysis, occurring in, depending on the definition used, 1.7–8.0% of treated patients. (NINDS, 1995; Albers *et al.*, 2000; Hacke *et al.*, 2004, 2008; Hill and Buchan, 2005; Wahlgren *et al.*, 2007). The three symptomatic intracranial haemorrhage definitions are the

NINDS (1997b), the ECASS III (Hacke *et al.*, 2008), and the SITS-MOST (Wahlgren *et al.*, 2007).

Pooled data of 2775 patients in the large randomized (ATLANTIS, ECASS and NINDS) trials showed a symptomatic intracranial haemorrhage rate of 5.9% for rt-PA treatment versus 1.1% for placebo ( $P < 0.0001$ ) (Hacke *et al.*, 2004). Similarly, meta-analysis of 2639 rt-PA for acute ischaemic stroke patients in general clinical practice showed a symptomatic intracranial haemorrhage rate of 5.2% (Graham, 2003). SITS-MOST's analysis of 31 627 intravenous thrombolysis patients identified nine independent risk factors for symptomatic intracranial haemorrhage: baseline NIHSS, serum glucose, systolic blood pressure, age, body weight, onset-to-treatment time, aspirin or combined aspirin and clopidogrel, and history of hypertension, with an overall symptomatic intracranial haemorrhage rate of 1.8% (Wahlgren *et al.*, 2007). Other factors include signs of mass effect, brain oedema, hypodensity or extensive early infarct change on pre-treatment brain imaging (Larrue *et al.*, 1997; NINDS, 1997a, b; Lansberg *et al.*, 2007; Saver and Yafeh, 2007), permeability changes detected on MRI (Kakuda *et al.*, 2008), pretreatment diffusion weighted imaging lesion volume, and post-thrombolysis blood pressure (Butcher *et al.*, 2010).

Several scoring tools using both clinical and imaging parameters available before initiation of thrombolysis have been developed to predict risk of haemorrhagic transformation (HT) in acute ischaemic stroke patients treated with intravenous rt-PA. SITS symptomatic intracranial haemorrhage risk score, a 12 point score adapted from the SITS-ISTR, can easily be applied to predict symptomatic intracranial haemorrhage risk after intravenous rt-PA—a score  $\geq 10$  is associated with a  $> 70$ -fold increased symptomatic intracranial haemorrhage rate compared to a score of 0 (Mazya *et al.*, 2012). The iScore, HAT and ASPECTS, discussed above, have also been validated in predicting HT risk (Barber *et al.*, 2000; Lou *et al.*, 2008; Saposnik *et al.*, 2012a). Additionally, the SEDAN score, ranging from 0 to 6 points, consists of baseline blood Sugar, Early infarct signs and hyperDense cerebral artery sign, Age and baseline NIHSS. It is used for assessing risk of

### Box 2 Quantitative metrics in predictive clinical scoring systems

Metrics	Scales		
	Dragon	iScore	HAT
Age	Yes	Yes	
Onset-to-treatment time	Yes		
Blood glucose	Yes	Yes	Yes (+ history of diabetes)
Blood pressure			
Stroke severity	Yes (NIHSS)	Yes	Yes (NIHSS)
Imaging changes	Yes (EIC/HMCAS)		Yes (EIC)
Comorbidities	Yes (mRS)	Yes (CV risk factors, comorbid conditions, preadmission disability)	
Additional factors:		Gender, stroke subtype	
Predicts:	IVT outcome	30-day mortality/disability/ institutionalization 1 year mortality	Long-term outcome sICH risk

(Lou *et al.*, 2008; Strbian *et al.*, 2011; Saposnik *et al.*, 2012).

mRS = modified Rankin Score; HAT = hemorrhage after thrombolysis; IVT = intravenous thrombolysis; CV = cardiovascular; sICH = symptomatic intracerebral haemorrhage.

symptomatic intracranial haemorrhage in intravenous thrombolysis patients with anterior and posterior circulation acute ischaemic stroke (Strbian *et al.*, 2012).

## Non-responders to rt-PA

Despite the proven benefits of rt-PA in patients with acute ischaemic stroke, only about half of patients respond to intravenous thrombolysis (Rha and Saver, 2007; Hacke *et al.*, 2008; Lees *et al.*, 2010). Clinical response may be affected by a number of factors, including location and extent of arterial occlusion, collateral integrity and characteristics of the clot itself such as burden, age and composition (Tan *et al.*, 2007; Fernandez-Cadenas *et al.*, 2009; von Kummer, 2010). These factors are important in predicting non-response to rt-PA, and may be helpful in choosing other reperfusion techniques.

### Site of arterial occlusion

Patients with terminal internal carotid artery occlusion, proximal middle cerebral artery occlusion, or tandem lesions might have a poor clinical response to rt-PA (Saqqur *et al.*, 2007b). A study of intravenous thrombolysis for acute ischaemic stroke patients found the rate of complete recanalization to be 44.2% for distal middle cerebral artery (favourable outcome, modified Rankin Score  $\leq 1$  at 3 months = 52%), 30% for proximal middle cerebral artery (25%), 5.9% for terminal internal carotid artery (18%), 27% for tandem cervical internal carotid artery/middle cerebral artery (21%), and 30% for basilar artery occlusion (25%) (Saqqur *et al.*, 2007b). Although continuous transcranial monitoring was a positive predictor for complete recanalization, pre-rt-PA NIHSS, glucose, systolic blood pressure and thrombolysis in brain ischaemia (TIBI) flow grade at the occlusion site were negative independent predictors. Patients with dampened flow (TIBI 3) at the occlusion site had higher odds of complete recanalization than those with no demonstrable residual flow signals (TIBI 0).

### Collateral integrity

Transcranial Doppler flow findings at the site of intracranial occlusion can predict the clinical response to intravenous thrombolysis—patients with lack of residual flow have a low probability of complete recanalization and recovery after intravenous thrombolysis (Labiche *et al.*, 2003; Saqqur *et al.*, 2009). In an earlier study of pretreatment transcranial Doppler, patients with no detectable residual flow signals had a <20% chance for complete early recanalization with intravenous thrombolysis (Labiche *et al.*, 2003). In another study of transcranial Doppler-detected residual flow with TIBI grading before intravenous rt-PA bolus in patients with proximal arterial occlusion, 17.7% of patients with TIBI 0, 33.1% with TIBI 1, 38.2% with TIBI 2 and 47.7% with TIBI 3 had achieved complete recanalization ( $P < 0.001$ ). Negative independent predictors of complete recanalization were high NIHSS, glucose, systolic blood pressure and lower TIBI grades. Poor outcome rate at 3 months (modified Rankin Score  $> 2$ ) was 61.3% in patients with TIBI 0, 56.9% for TIBI 1, 51.5% for TIBI 2, and 33.9% for TIBI 3 ( $P = 0.012$ ) (Saqqur *et al.*, 2009).

## Clot burden

Studies have demonstrated a relationship between the clot burden and recanalization (Tan *et al.*, 2009). More proximal occlusions have been found to carry greater thrombus burden (Saqqur *et al.*, 2007b). Using a CT angiogram grading system, the clot burden score is a 10-point scoring system developed to quantify thrombus burden (i.e. presence of contrast opacification on CT angiography) in a large cohort of patients with anterior circulation acute ischaemic stroke. Two points are subtracted for thrombus found in each of: the proximal M1 segment of the middle cerebral artery trunk, the distal M1 segment, and the supraclinoid internal carotid artery. One point is subtracted for thrombus found in each of the M2 branches, A1, and the infraclinoid internal carotid artery. A score of 10 is normal (clot absent), whereas a score of 0 implies complete multisegment vessel occlusion. Clot burden score  $< 10$  was associated with reduced odds of independent functional outcome (OR 0.09 for clot burden score  $\leq 5$ ; OR 0.22 clot burden score 6–7; OR 0.48 clot burden score 8–9; all versus clot burden score 10;  $P < 0.02$  for all). Lower clot burden scores were associated with lower follow-up ASPECTS ( $P < 0.001$ ) and higher parenchymal haematoma rates ( $P = 0.008$ ) (Puetz *et al.*, 2008a). Another study found clot burden score and collateral score to be useful additional important markers predicting clinical and radiological outcomes. Higher clot burden score and collateral score demonstrated smaller pretreatment perfusion defects and final infarct volume and better clinical outcome ( $P < 0.01$ ) (Tan *et al.*, 2009).

### Clot composition and age

Clot age and composition of thromboembolic material are factors likely to predict response to rt-PA therapy (Fulgham *et al.*, 2004; Kim *et al.*, 2006). Non-contrast CT measurement of thrombus composition based on Hounsfield units may be helpful in predicting response to intravenous thrombolysis: thrombus with lower Hounsfield units count on non-contrast CT (platelet-rich) is more resistant to lysis than thrombus with higher Hounsfield units count (erythrocyte-rich) (Kirchhof *et al.*, 2004; Kim *et al.*, 2006). Emboli composed of cholesterol, calcium, calcific plaque, fat or clots containing other debris may be resistant to enzymatic degradation by rt-PA (Halloran and Bekavac, 2004). Thrombolytics are also less effective in treating both mature embolic clots, due to excessive cross-linking (Fulgham *et al.*, 2004), and hyperacute thromboemboli, which are platelet-rich (Fulgham *et al.*, 2004).

## Other thrombolytics

Although alteplase (rt-PA) is currently the only approved thrombolytic agent for acute ischaemic stroke treatment, its limited fibrin specificity and possible neurotoxicity have fueled the search for other plasminogen activators. Newer thrombolytics with potentially improved half-life, higher target specificity and better safety profile are being evaluated in clinical trials. A phase 2B trial found significantly greater reperfusion ( $P = 0.004$ ) and better clinical outcomes ( $P < 0.001$ ) at 24 h in patients given tenecteplase versus alteplase  $< 6$  h after acute ischaemic stroke onset (Parsons *et al.*, 2012). Similarly, the phase 2 desmoteplase in acute ischaemic stroke (DIAS) and Dose Escalation Study of Desmoteplase in Acute

Ischaemic Stroke (DEDAS) trials demonstrated promising results with desmoteplase given 3–9 h after stroke onset (Hacke *et al.*, 2005; Furlan *et al.*, 2006), but the phase 3 DIAS-2 did not show any clinical benefit at 3 months (Hacke *et al.*, 2009). However, DIAS-3, DIAS-4, and DIAS-J are currently ongoing (NCT00790920, NCT00856661, NCT01104467) (ClinicalTrials.gov). Other examples with trials in progress include reteplase, plasmin and microplasmin. These have been extensively reviewed elsewhere (Balami *et al.*, 2013a).

## Interventional endovascular therapies

### Intra-arterial thrombolysis

Intra-arterial thrombolysis is another method for administering thrombolytic agents with several theoretical advantages over intravenous thrombolysis (Table 3). Intra-arterial thrombolysis is normally indicated for patients presenting within 6 h, those with large vessel occlusion like distal internal carotid artery and proximal middle cerebral artery, those with contraindications to intravenous rt-PA such as anticoagulated or postoperative patients, and those patients who do not improve after intravenous thrombolysis (Natarajan *et al.*, 2009). The Prolyse in Acute Cerebral Thromboembolism (PROACT II) trial compared intra-arterial thrombolysis (with pro-urokinase) to heparin-only controls in acute ischaemic stroke patients. The intra-arterial thrombolysis group had significantly higher recanalization rates and more favourable outcomes (modified Rankin Score 0–2) at 3 months, with similar mortality but a 5 × higher risk of intracerebral haemorrhage within 24 h of stroke onset (Furlan *et al.*, 1999), which was attributed to the longer (6 h) time window, as well as greater baseline stroke severity. Despite these encouraging results (adjusted relative risk 15%, number needed to treat = 7), the FDA did not approve intra-arterial pro-urokinase for acute ischaemic stroke, requesting a confirmatory trial that has never been performed. Nevertheless, the success of PROACT II has led to a new era in intra-arterial thrombolysis for acute ischaemic stroke treatment.

In subsequent analysis of the PROACT II data, the patients were stratified by baseline ASPECTS, showing a significant adjusted relative risk of independent functional outcome at 3 months in patients with ASPECTS >7, relative to those with ASPECTS ≤7 (adjusted relative risk 3.2, CI 1.2–9.1 versus adjusted relative risk 1.0, CI 0.6–1.9), highlighting the importance of quantitative imaging metrics for patient selection in future intra-arterial thrombolysis trials (Hill *et al.*, 2003b).

Meta-analysis of five randomized trials suggests that intra-arterial fibrinolysis substantially increases recanalization rates with good and excellent clinical outcomes relative to control (generally intravenous heparin) in acute ischaemic stroke (Lee *et al.*, 2010), and in open clinical case series intra-arterial therapy had higher early recanalization rates (50–80%) than intravenous thrombolysis (30–50%) (Alexandrov *et al.*, 2004). In addition to the benefit of intra-arterial therapy for treatment of acute ischaemic stroke due to

middle cerebral artery occlusion (Fields *et al.*, 2011), there is also evidence of benefit of intra-arterial therapy in vertebral or basilar occlusions up to 24 h after symptom onset (Macleod *et al.*, 2005), with higher rates of recanalization in vertebrobasilar occlusion with intra-arterial therapy than intravenous thrombolysis (65 versus 53%) (Lindsberg and Mattle, 2006).

The majority of these favourable intra-arterial therapy studies used recombinant pro-urokinase. Unfortunately, recombinant pro-urokinase is currently not available for routine clinical use and intra-arterial therapy with rt-PA is not substantiated by randomized controlled trials, only observational and non-randomized data. Although intra-arterial rt-PA and urokinase are not approved by the FDA for acute ischaemic stroke treatment, some specialist centres have adopted protocols for their use in specific cases (Ahn *et al.*, 2006; Sacco *et al.*, 2007; Smith, 2007; Alberts *et al.*, 2008).

### Ultrasound enhanced therapies (sonothrombolysis)

Ultrasound enhanced thrombolysis represents a new therapeutic approach that holds promise for improving recanalization rates and outcome. The mechanism of ultrasound enhanced thrombolysis involves reversible alteration of fibrin structure and microcavity formation in the shallow layers of thrombus, allowing increased penetration of alteplase into the clot and enhancing flow with microstreaming and vessel dilation (Suchkova *et al.*, 1998; Alexandrov and Grotta, 2002; Labiche *et al.*, 2003; Rubiera *et al.*, 2005).

In the Combined Lysis of Thrombus in Brain Ischaemia Using Transcranial Ultrasound and Systemic rt-PA (CLOT-BUST) trial, continuous 2 MHz transcranial Doppler ultrasonography applied for 2 h augmented the rate of rt-PA induced arterial recanalization (Alexandrov *et al.*, 2004). A meta-analysis of six randomized and three non-randomized studies of ultrasound enhanced thrombolysis in acute ischaemic stroke showed that the likelihood of complete recanalization was higher in patients receiving the combination of transcranial Doppler with intravenous thrombolysis compared with intravenous thrombolysis alone (pooled OR 2.99, CI 1.70–5.25,  $P = 0.0001$ ) (Tsvigoulis *et al.*, 2010). A pilot study showed enhanced recanalization and a trend toward better short- and long-term outcome with a combination of microbubbles (small microspheres filled with air or gas) and ultrasound enhanced thrombolysis compared with ultrasound enhanced thrombolysis or intravenous thrombolysis alone (Molina *et al.*, 2006). Further phase 3 trials of combined ultrasound enhanced thrombolysis and intravenous thrombolysis are planned (NCT01098981) (ClinicalTrials.gov).

### Mechanical thrombectomy

The need for a wider therapeutic window to increase the proportion of acute ischaemic stroke patients who receive treatment has led to the advancement of endovascular intervention through mechanical thrombectomy, restoring cerebral blood flow by either removing or fragmenting the obstructing thrombus, with the theoretical advantage, over pharmacological thrombolysis, of

**Table 3** Different modalities for recanalization of occluded cerebral vessels

Mode of treatment	Advantages	Disadvantages	Recanalization rates
Pharmacological thrombolytic therapy Intravenous rtPA	Immediate delivery, wide availability Does not require highly specialized equipment or technical expertise Rapid local delivery Direct infusion of small dose but higher concentration of thrombolytic agent into the thrombus Lower systemic concentration and reduced systemic side effects Exact knowledge of timing and degree of recanalization achieved Recanalization rate may be higher than with intravenous rtPA Advantages of intra-arterial therapy appear to be greatest for intracranial intracerebral artery, carotid terminus and proximal middle cerebral artery occlusions	Time constraints Higher systemic concentration and greater risk of haemorrhagic complication Time delay required for cerebral angiogram and microcatheter positioning before initiating thrombolytic infusion Complex procedure Labor and capital intensive Potentially increased vulnerability to haemorrhage incidence due to manipulation of catheter within vessels and requirement for heparin administration intra- procedurally to deter catheter-induced thrombosis Low availability, as reserved for specialized centres with neuro-interventional team.	46.2% 63.2%
IVT and IAT			67.5%
Mechanical thrombectomy Retrieval devices The Merci Retriever System The Phenox clot retriever The Alligator Retriever The Trevo Device	Real-time visualization of thrombus Faster recanalization over pharmacological thrombolysis May be more efficacious at achieving full recanalization Lower intracerebral and systemic haemorrhage risk because of the avoidance of pharmacological lysis More effective in removing large thrombi in proximal vessels, such as carotid T occlusion, where the volume of clot may not be easily dissolved through enzymatic degradation by pharmacological lysis Effective for non-responders to rtPA Effective for material resistant to pharmacological lysis such as excessively cross-linked mature embolic clots as well as emboli composed of calcium, cholesterol or other debris	Low rate of complete recanalization and increased rate of intracerebral haemorrhage.  Requires bulky catheters that may cause endothelial damage, vessel wall perforation or rupture. vessel dissection, intracranial bleeding, and subarachnoid haemorrhage. Fragmented thrombus can cause distal embolization Risk of groin haemorrhage Highly labour and capital intensive and limited to specialist centres	83.6%
Aspiration devices Penumbra			

(continued)

Table 3 Continued

Mode of treatment	Advantages	Disadvantages	Recanalization rates
Stenting and angioplasty The WINGSPAN Stent Solitaire stent Revive Device	May be suitable in patients at high risk for haemorrhage with thrombolytic drugs (e.g. after cardiac surgery) Higher rate of recanalization and potential to achieve immediate recanalization.	Risk of early re-thrombosis as clot is only pressed to the vessel wall and not removed from the occluded vessel Use of aggressive antiplatelet therapy after placement, which can increase the risk of haemorrhagic conversion of infarcts, or the risk of reperfusion haemorrhage Later in-stent stenosis	
Multimodal reperfusion therapy	Quick reperfusion and higher rates of recanalization		

IAT = intra-arterial thrombolytic therapy; IVT = intravenous thrombolysis.

avoiding systemic bleeding risks (Table 3). Mechanical thrombectomy offers the promise of efficacious treatment for patients who failed recanalization after thrombolysis, or in patients with pharmacological thrombolysis contraindications, such as recent surgery, abnormal haemostasis, or late presentation/unknown time of onset (Smith *et al.*, 2005b, 2008; Nogueira and Smith, 2009). It is also usually indicated for large clot burdens or for clots containing large amounts of calcium, cholesterol or other debris resistant to thrombolytics (Halloran and Bekavac, 2004).

A myriad of devices have been developed, including retriever devices (e.g. Merci) (Smith *et al.*, 2005b), Phenox (Henkes *et al.*, 2006; Liebig *et al.*, 2008), Alligator (Kerber *et al.*, 2007), Revive (Rohde *et al.*, 2011) and Trevo (Wahlgren, 2012), deployed distal to a thrombus for clot extraction, aspiration devices (e.g. Penumbra) (Bose *et al.*, 2008), which apply a vacuum to the proximal aspect of the thrombus, with a potentially lower rate of embolic events (Nguyen *et al.*, 2011), and stents (e.g. balloon angioplasty and stents) (Ueda *et al.*, 1998; Nakano *et al.*, 2002, 2004; Gupta *et al.*, 2006a; Levy *et al.*, 2006; Nogueira *et al.*, 2008), and self-expandable stents such as Wingspan (Levy *et al.*, 2009) and Solitaire (Roth *et al.*, 2010; Koh *et al.*, 2012). Stent retrievers (e.g. Trevo) are preferred under current AHA guidelines. Currently four devices have FDA clearance: Merci, Penumbra, Solitaire, and Trevo (Jauch *et al.*, 2013).

## Endovascular versus intravenous thrombolysis approaches

The Local versus Systemic Thrombolysis for Acute Ischemic Stroke (SYNTHESIS expansion) trial showed no benefit of endovascular treatment (pharmacological or mechanical intervention or both, at clinician's discretion) alone over intravenous thrombolysis alone (Ciccone *et al.*, 2013). Similarly, the Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) study, designed to identify people who might benefit from mechanical embolectomy using multimodal CT or MRI (NCT00389467) (ClinicalTrials.gov), found embolectomy not to be significantly superior to standard care (intravenous thrombolysis) in patients with 'favourable' penumbral pattern or non-penumbral pattern, or overall (Kidwell *et al.*, 2013). These results suggest the need for development of better endovascular therapies, or better patient selection strategies through meta-analysis of baseline patient metrics, but current evidence does not support endovascular therapy in acute ischaemic stroke patients eligible for intravenous thrombolysis (Jauch *et al.*, 2013).

## Bridging therapies: combination of intravenous and endovascular approaches

Although both intravenous thrombolysis and endovascular strategies to recanalize could each be effective, the combination of

these methods could be more synergistically beneficial following acute ischaemic stroke.

### Combined intravenous thrombolysis–intra-arterial therapy

Combination therapy, also known as bridging therapy, is another approach to improved vessel recanalization through the early use of intravenous thrombolysis followed by local intra-arterial therapy. Bridging therapy potentially combines the advantages of each modality: the wide availability of early rapid intravenous thrombolysis and the potentially higher recanalization rates of intra-arterial therapy, allowing for better clinical outcomes in acute ischaemic stroke. The first pilot study of bridging therapy was the Emergency Management of Stroke (EMS) Bridging trial, a multicentre randomized controlled trial. Although recanalization of middle cerebral artery occlusions was greater with a combined intravenous/intra-arterial approach (82%) than with intra-arterial therapy alone (50%), with lower NIHSS at 3 months, there was a significantly higher mortality in the bridging therapy group (29% versus 5.5%), but the risk of symptomatic intracranial haemorrhage in both groups was similar (Lewandowski *et al.*, 1999). Subsequent Interventional Management of Stroke (IMS I and II) trials demonstrated improved outcomes at 3 months with bridging therapy compared with NINDS' historical placebo-treated controls (IMS, 2004, 2007), although it would have been more appropriate to compare outcomes to current standard of care (i.e. intravenous thrombolysis). Recanalization rates of 56% in IMS I and 60% in IMS II, and symptomatic intracranial haemorrhage rates of 6.3% in IMS I and 11.8% in IMS II (IMS, 2004, 2007), led to IMS III, meant to assess whether bridging therapy is superior to intravenous thrombolysis alone when initiated within 3 h of onset. However, the study was stopped early, following Data and Safety Monitoring Board recommendation, because of futility. No serious safety concerns were identified, but the bridging therapy and intravenous thrombolysis patients had no significant difference in functional independence (modified Rankin Score  $\leq 2$ ) at 3 months, symptomatic intracranial haemorrhage rate, or mortality (Broderick *et al.*, 2013).

In a recent meta-analysis of 15 studies using bridging therapy the pooled estimate was 69.6% (CI 63.9–75.0%) for recanalization rate, 48.9% (CI 42.9–54.9%) for favourable outcome, 8.6% (CI 6.8–10.6%) for symptomatic intracranial haemorrhage, and 17.9% (CI 12.7–23.7%) for mortality (Mazighi *et al.*, 2012). Current evidence does not necessarily support bridging therapy in patients eligible for intravenous thrombolysis, absent better patient selection strategies.

### Combined intravenous thrombolysis–mechanical thrombectomy

The REcanalization using Combined intravenous Alteplase and Neurointerventional ALgorithm for acute Ischemic Stroke (RECANALIZE) study, demonstrated higher recanalization rates in the combined intravenous thrombolysis–endovascular group (87%) (using intra-arterial alteplase, and mechanical procedures—snare or balloon angioplasty—if intra-arterial therapy failed) than in the intravenous thrombolysis alone group (52%) (adjusted relative

risk 1.49, CI 1.21–1.84,  $P = 0.0002$ ). The combined approach suggested advantages over intravenous thrombolysis alone in early neurological improvement (NIHSS  $\leq 1$  or a  $\geq 4$  point improvement) at 24 h (60 versus 39%; adjusted relative risk 1.36, CI 0.97–1.91,  $P = 0.07$ ) and favourable outcome (modified Rankin Score 0–2) at 3 months (57 versus 44%; adjusted relative risk 1.16, CI 0.85–1.58,  $P = 0.35$ ), although the symptomatic intracranial haemorrhage rate (9 versus 11%) and 90 day mortality (17% in both) were similar. (Mazighi *et al.*, 2009). The Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE) is a planned randomized controlled trial to investigate whether additional mechanical thrombectomy can improve functional outcome in acute ischaemic stroke patients with large artery occlusion given intravenous thrombolysis as standard care (NCT01745692) (ClinicalTrials.gov).

### Multimodal reperfusion therapy

Multimodal reperfusion therapy is another approach, combining pharmacological and several endovascular methods to achieve quick reperfusion and higher rates of recanalization after acute ischaemic stroke. Combining approaches, including mechanical thrombolysis, intra-arterial lytic drugs, clot retrieval, and angioplasty with stenting, is increasingly being used in some centres (Lin *et al.*, 2003; Abou-Chebl *et al.*, 2005; Gupta *et al.*, 2006b; Leker *et al.*, 2009; Cohen *et al.*, 2011; Park *et al.*, 2012). Evidence of the benefits of multimodal reperfusion therapy in improving recanalization is derived from case reports of middle cerebral artery and extracranial internal carotid artery occlusions with varying results (Abou-Chebl *et al.*, 2005; Gupta *et al.*, 2006b; Bunc *et al.*, 2010). This approach is particularly promising for patients with large hemispheric infarcts (Leker *et al.*, 2009), posterior circulation stroke, and basilar artery occlusion (Raphaelli *et al.*, 2009), where high survival and good outcome rates have been demonstrated (Leker *et al.*, 2009; Raphaelli *et al.*, 2009).

Multimodal reperfusion therapy has been found to be safe and effective at recanalizing occluded cerebral vessels that fail to respond to thrombolysis, without increasing the risk of intracerebral haemorrhage (Abou-Chebl *et al.*, 2005). In case series involving 12 patients in whom intravenous thrombolysis had failed, multimodal reperfusion therapy, consisting of GPIIb/IIIa antagonists, angioplasty and mechanical embolectomy, resulted in good recanalization in 11 patients, with only one patient at low perfusion post-multimodal reperfusion therapy. There was only one symptomatic intracranial haemorrhage, and half of patients had a favourable outcome (NIHSS  $\leq 4$ ) at discharge (Abou-Chebl *et al.*, 2005). Further research into multimodal reperfusion therapy is warranted as the evidence for its benefit and safety is based only on case series.

## Conclusion

*'...and he preferred to know the potencies of herbs, and the practice of healing, and to ply this quiet art, resigning fame.'* (Virgil, 19 BCE).

Thrombolysis using rt-PA remains the only approved treatment for acute ischaemic stroke. Rt-PA changed the world, not just of

stroke treatment, but of neurology in general. The availability of an effective therapy has dramatically changed the management of patients presenting with neurological symptoms, leading to quick assessment and application of therapeutic protocols in those patients with a high diagnostic probability of stroke. Evidence is now accumulating for its benefit in clinical practice, both within standard guidelines and potentially outside them. By combining both clinical and imaging criteria, patient selection can be improved, enhancing the benefits while reducing the risk of complications. The main clinical parameters are age, NIHSS, serum glucose, systolic blood pressure and onset-to-treatment time. ASPECTS, a widely used and validated tool, can be used to standardize and quantify imaging analysis to predict clinical outcome.

Although there is evidence from randomized controlled trials for the benefit of intravenous thrombolysis or other acute interventions in restoring blood flow and salvaging the ischaemic penumbra following acute ischaemic stroke, there remains a need for trials and meta-analyses to help provide additional evidence-based guidelines. These will help in patient selection, determining when the benefits outweigh the risks in those patients that fall into the exclusionary areas surrounding the current guidelines, such as onset-to-treatment times >4.5 h, seizure at stroke onset, anticoagulation, or mild/rapidly improving symptoms. Likewise, little is known about the risk of thrombolysis in conditions that fall into therapeutic 'grey areas' such as wake-up stroke/stroke of indeterminate onset, dementia, malignancy, and pregnancy, as these patients are often excluded from clinical trials and observational studies. The relatively disappointing results of the studies comparing intra-arterial therapy to intravenous thrombolysis may be due to improper patient stratification. Meta-analysis is warranted to see if the established quantitative metrics, particularly imaging scoring systems, can identify subgroups of patients who can potentially benefit.

More research will hopefully lead to the identification and inclusion of a greater number of suitable patients for thrombolysis, maximizing the number benefiting from rt-PA therapy. Evidence-based support for definite exclusion criteria is valuable, but must be adaptable to an acute clinical setting—stringent additional testing for rigorous exclusion of potential stroke mimics can be counterproductive if it results in closure of the therapeutic time window.

Patient selection is both science and art. The science arises from meta-analysis of the predictive value of quantitative metrics in determining response to therapy. The art arises from the gradual accumulation of clinical experience that reassures the clinician that they are treating the patient not just because they can, but because they expect to see a real benefit.

The chemical neurosurgery that rt-PA provides is the most validated tool in our arsenal of acute ischaemic stroke treatments. Despite the advent of several endovascular approaches, intravenous thrombolysis remains the treatment of choice in eligible patients. Only by combining thrombolysis with the quiet art of patient selection can we ameliorate outcomes for patients who may fall outside the guidelines, or in the many grey areas within the standard guidelines, and identify the patients that truly have the best chance of a positive outcome.

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