Review

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Treatment of acute stroke: an update

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Abstract. Mikulik R, Wahlgren N (St. Anne's University Hospital in Brno, Brno; Masaryk University, Brno; Karolinska Institutet, Stockholm; and Karolinska University Hospital, Stockholm, Sweden). Treatment of acute stroke: an update (Review). *J Intern Med* 2015; **278**: 145–165.

Stroke is the second leading cause of global mortality after coronary heart disease, and a major cause of neurological disability. About 17 million strokes occur worldwide each year. Patients with stroke often require long-term rehabilitation following the acute phase, with ongoing support from the community and nursing home care. Thus, stroke is a devastating disease and a major economic burden on society. In this overview, we discuss current strategies for specific treatment of stroke in the acute phase, focusing on intravenous thrombolysis and mechanical thrombectomy. We will consider two important issues related to intravenous thrombolysis treatments: (i) how to shorten the delay between stroke onset and treatment and (ii) how to reduce the risk of symptomatic intracerebral haemorrhage. Intravenous thrombolysis has been approved treatment for acute ischaemic stroke in most countries for more than 10 years, with rapid development towards new treatment strategies during that time. Mechanical thrombectomy using a new generation of endovascular tools, stent retrievers, is found to improve functional outcome in combination with pharmacological thrombolysis when indicated. There is an urgent need to increase public awareness of how to recognize a stroke and seek immediate attention from the healthcare system, as well as shorten delays in prehospital and within-hospital settings.

Keywords: acute stroke therapy, intravenous thrombolysis, mechanical thrombectomy, neurointervention, stroke.

Introduction

Globally, about 17 million strokes occur every year and stroke is the second leading cause of death after coronary heart disease [1, 2]. The true burden of stroke, however, also includes chronic disability [2]. Patients with stroke often require extended stays in hospital followed by rehabilitation, ongoing community support and care in a nursing home. Thus, stroke is a huge economic burden on society. Furthermore, stroke is a main cause of neurological disability, not only in the elderly, but also in younger age groups: in 2010, 31% of strokes occurred in children and adults below 65 years of age [2].

Although improved prevention and healthier lifestyles have resulted in a decrease in age-adjusted stroke incidence, the total number of strokes is expected to increase because of an increase in the elderly population in industrialized countries [2]. In Sweden, the proportion of the population over the age of 70, which was 13% in the year 2000, is expected to rise to 20% in 2050 [3]. In developing countries such as India, which has an annual stroke rate of 1.6 million, improved health care may contribute to increased identification of stroke events. It is predicted that stroke will account for 6.2% of the total burden of illness in developed countries in 2020 [4]. Thus, without major advances in prevention, acute stroke treatment and rehabilitation, the cost of this disease will increase dramatically.

Here, we will review current strategies for specific treatment of stroke in the acute phase. However, it is beyond the scope of this overview to consider nonspecific strategies, including management of blood pressure, glucose and temperature, as well as management of prehospital and postacute stroke care.

Strategies to reduce the acute stroke lesion

Stroke is caused by cerebral infarction (85% of cases) or haemorrhage (the remaining 15%).

Symptom onset is typically sudden. After rupture of an artery in the brain, a haemorrhage usually increases in volume over several hours, causing damage to the brain tissue and elevating the intracranial pressure [5]. After occlusion of a cerebral artery, there is a double 'roll-out' of pathological events. An initial immediate decrease in blood flow in the occluded area (ischaemia) is followed by death of the ischaemic cells (infarct); the latter occurs within a few hours [6].

The location and the volume of the lesion determine the neurological symptoms, such as paresis (usually affecting one side of the body), sensory dysfunction, speech difficulties, blindness and double vision. Neurological symptoms subsequently determine the functional outcome, which depends on the ability to perform basic activities of daily living such as eating, dressing, grooming and using the toilet, as well as more advanced work, leisure or social activities (Fig. 1). Functional outcome is usually graded between 0 and 6 on the modified Rankin scale (mRS) score, with 0 indicating normal functional status and 6 indicating fatal outcome. Functional independence for activities of daily living corresponds to an mRS score of 0–2; a score of 0–1 is usually classified as an excellent functional outcome.

Associations between lesion volume, neurological symptoms and functional outcome have been shown for both haemorrhagic and ischaemic strokes [5, 7, 8].

The size of the stroke lesion, haemorrhage or infarction, determines the final outcome (Fig. 2). Larger infarcts are associated with increased severity of the neurological deficit and worse functional outcome, although volume is not the only determinant of the degree of the neurological deficit (Table 1). Infarction in the whole territory of the middle cerebral artery, causing a total anterior circulation syndrome (Table 1), is due to proximal occlusion of the artery and has a particularly bad prognosis with only 5% of patients showing functional independence after 1 year. Accordingly, the logical strategy is to intervene in the acute phase of stroke to limit the size of the stroke lesion, which becomes irreversible over the first few hours after the onset of symptoms [9]. Lesion growth can be reversed only by restoration of blood flow and only if such restoration is achieved early [10–12]. Therefore, modern treatment approaches require excellent infrastructure in terms of early identification of stroke symptoms and prehospital management, as well as highly professional and streamlined in-hospital care to achieve early restoration of blood flow. Increased public awareness about stroke symptoms and the importance of calling an ambulance without delay as well as efforts amongst hospitals to shorten delays in management suggest that this is possible. Important aspects of early-phase intervention are prevention of recurrent stroke, especially in patients after a transient ischaemic attack (TIA) or minor stroke [13], and facilitation of recovery programmes in patients after disabling stroke [14]. Several important scientific issues in this area still need to be addressed.

Currently, intravenous thrombolysis is the only generally accepted pharmacological treatment for acute ischaemic stroke and is therefore recommended as evidence-based treatment in stroke guidelines [15]. Mechanical thrombectomy substantially improves functional outcome and may reduce mortality without increasing the risk of

Fig. 1 *Functional outcome of stroke. The functional outcome is the clinically relevant outcome of stroke treatment interventions, that is restoration of normal functions and abilities and, at least, avoidance of dependence on the help of others for daily living activities. The functional outcome is dependent on the degree of neurological dysfunction, such as paresis of one side of the body or inability to speak or understand spoken language. The degree of neurological dysfunction is dependent on the extent of neurological damage in the brain. This damage develops over the first few hours after stroke onset, which is typically sudden.*

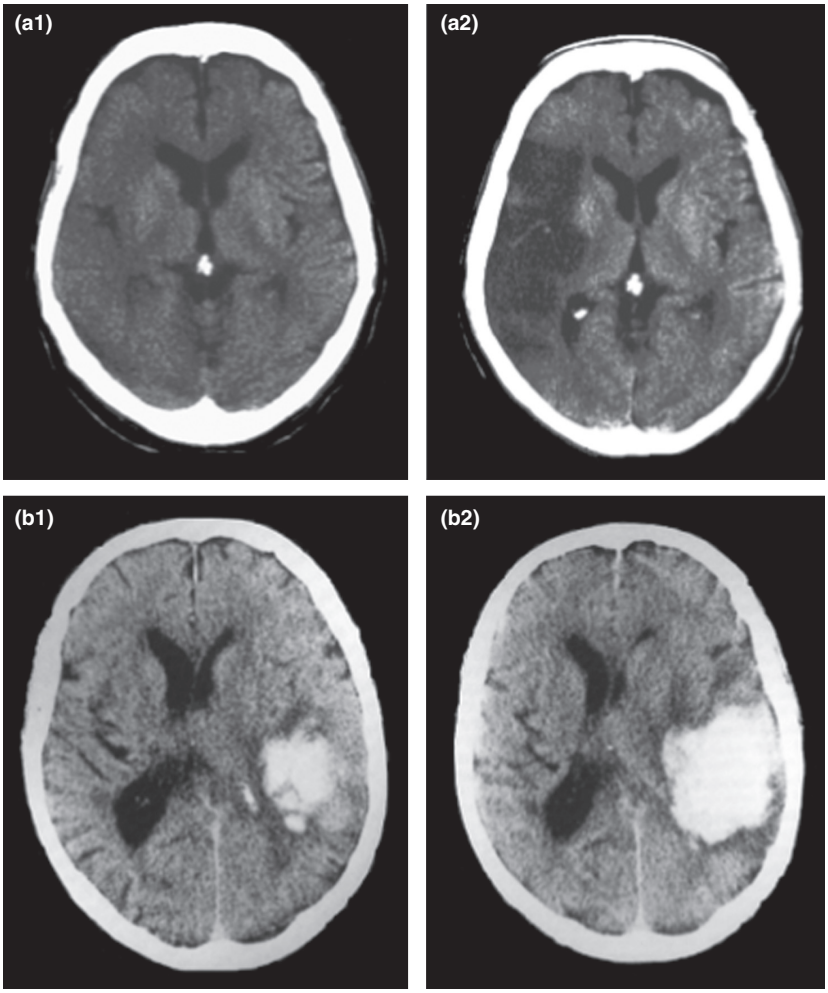

Fig. 2 *Computed tomography images at approximately 3 h after stroke onset (a1 and b1) and at approximately 24 h (a2 and b2) in a patient with developing cerebral infarction (a1 and a2) and a patient with cerebral haemorrhage (b1 and b2). Saver has calculated that in a typical large-vessel acute ischaemic stroke, about 1.9 million neurons die every minute during which stroke is untreated [27].*

haemorrhagic complications [16–20]. Decompressive surgery for malignant cerebral infarcts, at least in patients under the age of 60 years, is now also well-documented and recommended therapy [21]. There is also considerable evidence to support the admission of patients with stroke to specialized stroke units [22]. Aspirin has been used for many years to initiate the prevention of early stroke recurrence [23, 24], and there is recent evidence of the benefit of dual antiplatelet therapy [25], as discussed below. An overview of strategies to reduce the development of the stroke lesion and its consequences is presented in Table 2.

Reperfusion to treat ischaemic stroke

Thromboembolic occlusions of large cerebral arteries cause around 65% of all strokes, that is almost 11 million every year globally [1, 2, 7]. The reduction in blood flow resulting from an artery occlusion can be compensated by collateral blood flow over the surface of the brain, originating from other main cerebral arteries (Fig. 3) [9, 26]. Because this collateral blood flow usually only partially compensates for the main supply lost by the occlusion, flow will gradually decrease from the surface of the brain (where it may be close to normal) to the deeper parts of the territory. If blood flow is not reduced below 20 mL/100 g min^{-1} (i.e. 40% of a normal flow of 50 mL/100 g min^{-1}), the effect will be limited because of a compensating increase in oxygen extraction from blood [9]. However, below this level, neurotransmission will cease, resulting in neurological symptoms. Cells may survive for minutes or hours, but will die if blood flow is not restored, resulting in an infarct. On average, 1.9

Table 1 *Relation between volume of infarct, neurological deficit and functional outcome*

Place of artery occlusion	Median volume of infarct (mL)[a]	Neurological deficit/clinical syndrome	Functional outcome (%)[b]
Middle cerebral artery occlusion (proximal)	95	TACS: motor/sensory deficit; cognitive dysfunction (dysphasia/neglect); visual field defect	95
Middle cerebral artery occlusion (segment)	20	PACS: two of the above	45
Lenticulostriate (small) artery occlusion	2.5	LACS: motor/sensory deficit; no cognitive dysfunction; no visual field defects	35

[a]Data from Lindgren *et al.* [7]. [b]Percentage dead or dependent for daily life activities after 1 year; data from Bamford *et al.* [8].
Median volumes of infarcts are given for total anterior circulation syndrome (TACS; typical for proximal middle cerebral artery occlusion), partial anterior circulation syndrome (PACS; for branch occlusion of the middle cerebral artery) and for lacunar syndrome (LACS; for small artery/lenticulostriate artery occlusion).

million nerve cells die per minute of arterial occlusion [27].

Treatments to rapidly reopen an occluded artery are a priority in acute occlusive stroke because recanalization improves short- and long-term outcomes [28, 29]. If reopening occurs spontaneously and results in complete neurological recovery within the first 24 h, the event is defined as a TIA. However, if neurological dysfunction continues for several hours, patients may develop brain infarction as assessed by magnetic resonance imaging (MRI). TIA is therefore defined, according to the American Heart Association/American Stroke Association (AHA/ASA) and other professional bodies, as a transient episode of neurological dysfunction caused by focal brain, spinal cord or retinal ischaemia, without acute infarction [30–32].

Treatment strategies to reanalyse a thromboembolic occlusion include intravenous [11, 12, 33–43] or intra-arterial [44–47] thrombolysis, mechanical removal [16–20, 28, 48–50] and the use of ultrasound in addition to thrombolytic agents (i.e. sonothrombolysis) [51–53]. Only intravenous thrombolysis using the recombinant tissue plasminogen activator (tPA) alteplase is currently recommended treatment for acute ischaemic stroke [15].

Thrombolytic agents other than alteplase have been evaluated in trials although with limited success. The tPA duteplase [54] is used primarily in Japan; the use of streptokinase is generally avoided after evidence of an unfavourable benefit/safety balance [55–57]. Recent trials of desmoteplase [58] and ancrod [59] have not indicated a benefit.

Below, several reperfusion strategies are discussed in more detail: (i) intravenous thrombolysis with alteplase (proven therapy), (ii) endovascular treatment (recently proven but needs to be implemented in clinical practice) and (iii) a method of enhanced intravenous thrombolysis (not proven, investigational). Prevention of early stroke recurrence, which is routine clinical practice, is also described.

Intravenous thrombolysis with alteplase for acute ischaemic stroke

Intravenous thrombolysis with alteplase has been evaluated in nine randomized controlled trials [11, 12, 33–36, 42] and statistical overviews [10, 41, 43], and in two large postlaunch safety monitoring studies [39, 40, 60]. The first of these studies [11, 33–36] resulted in regulatory approval of intravenously administrated alteplase within 3 h after the onset of an ischaemic stroke, if cerebral haemorrhage was excluded by computer tomography (CT). In the EU, a condition for approval in 2002 was that all patients treated with alteplase for stroke should be registered in the Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS-MOST). Data from SITS-MOST, published in 2007 and 2008, confirmed that safety and efficacy were

Table 2 *Strategies to reduce the development of the stroke lesion and its consequences*

Stroke type	Strategies to reduce the stroke lesion volume and minimize complications		Current status	References
Any	Early identification of stroke diagnosis for faster onset of treatment intervention	Structured identification tests by ambulance dispatch operator	Under development; many local initiatives	[120–127]
	Organized inpatient care for stroke	Stroke units	Solid scientific evidence	[22]
Bleeding	Stop bleeding expansion	Recombinant coagulation factor VIIa	Clinical trials failed. Trials ongoing of ICH during anticoagulation	[115, 128]
	Evacuate bleeding	Stereotactic or open neurosurgery	In clinical use to some extent; large clinical trial failed. Trial ongoing of lobar intracerebral bleeding	[129]
Infarct	Reopening of occluded artery	IV thrombolysis[a]	Established therapy, based on trials, meta-analyses and registries; increased support for wider indications	[11, 12, 33–42]
		IA thrombolysis	One (interrupted) trial positive; three new reports of endovascular therapy, including IA thrombolysis neutral	[44–47]
		Mechanical extraction (thrombectomy)	In clinical use to some extent; Recent evidence of benefit of mechanical extraction with stent retrievers	[16–20, 28, 44–50]
		Ultrasound enhanced thrombolysis	Phase II trial showed more recanalization with ultrasound+ thrombolytics vs. thrombolytics alone. Phase III trial stopped for futility	[51–53]
	Optimization of metabolic factors	Optimizing blood pressure in hypertension	No conclusive evidence; trials ongoing	[130, 131]

Table 2 (*Continued*)

Stroke type	Strategies to reduce the stroke lesion volume and minimize complications		Current status	References
		Lowering blood glucose in hyperglycaemia	No conclusive evidence; trials ongoing	[132, 133]
		Lowering body temperature in hyperthermia/ normothermia	No conclusive evidence; body temperature usually normalized; cooling trials ongoing	[134–136]
	Prevention of early stroke recurrence, initiation in acute phase	Aspirin alone for ischaemic stroke from day 1 *or* aspirin combined with clopidogrel from day 1 for maximum of 90 days in high-risk TIA or minor stroke	Evidence from two Phase III trials for aspirin alone, one trial for combination with clopidogrel	[23–25]
	Block pathophysiological events in ischaemia	Neuroprotecting pharmacological agents	No conclusive evidence despite large number of trials. Some trials ongoing	[137, 138]
	Reduce mass effects and increase intracranial pressure caused by infarct oedema	Decompressive surgery in malignant MCA infarcts[a]	Established therapy for patients under age 60, new data for 60+ supportive	[139–143]

ICH, intracerebral haemorrhage; MCA, middle cerebral artery; IA, intra-arterial; IV, intravenous; TIA, transient ischaemic attack.
[a]Included in clinical guidelines as evidence-based treatments for some groups of patients.

maintained in clinical practice, compared to randomized trials [39, 40, 60]. Another condition of the EU regulatory body was that a randomized controlled trial of thrombolysis is conducted within the time window of 3–4.5 h after stroke onset.

Widening the treatment time window for thrombolysis

The outcome of the European Cooperative Acute Stroke Study (ECASS) III, a randomized controlled trial of thrombolysis within 3–4.5 h after stroke onset [12], provided evidence in favour of expanding the treatment time window from 3 h up to 4.5 h after stroke onset. The absolute difference in the primary outcome (mRS score of ≤1) between placebo and thrombolysis was 7.2%. Further evidence in support of extending the time period of treatment was provided by an observational study based on clinical practice data from the international multicentre database SITS International Stroke Thrombolysis Register (SITS-ISTR) [37, 40]. On the basis of these two studies, the European Stroke Organisation (ESO) changed the guidelines for management of acute ischaemic stroke and TIA after discussion at the Karolinska Stroke Update meeting in Stockholm, Sweden, in November 2008 [61, 62]. Furthermore, the AHA/ASA issued scientific advice on expansion of the time window for thrombolysis [63].

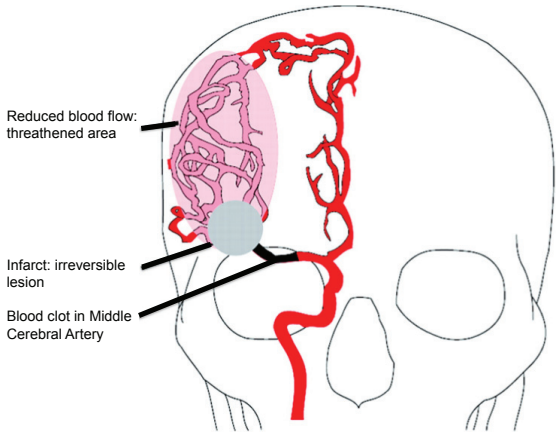

Fig. 3 *Collateral flow through leptomeningeal arteries. The blood flow reduction resulting from an artery occlusion can at least partly be compensated for by collateral blood flow over the surface of the brain, originating from other main cerebral arteries. Within the threatened area, cells die as long as the occlusion persists, and fever [134], hypotension [144], hypertension [80] and hyperglycaemia [132, 133] may accelerate cell death (Adapted from AJNR 27:728-735, 2006, with permission).*

Overall evaluation of treatment effect of thrombolysis and current recommendations

Findings from the most recent statistical overview of randomized trials of thrombolysis in stroke [43] indicate an absolute increase in disability-free survival of about 10% for patients treated within 3 h and about 5% for those treated between 3 and 4.5 h, despite an average absolute increased risk of early death from intracranial haemorrhage of about 2%. At present, professional societies recommend intravenous thrombolysis for patients with acute onset of stroke within 4.5 h, provided that haemorrhage or other contraindications are excluded on neuroimaging (e.g. CT or MRI) [11, 33]. Treatment indications are discussed in detail below (see Table 3).

Alteplase is the recommended treatment for ischaemic stroke

The recommended treatment for ischaemic stroke is an intravenous infusion of alteplase (Actilyse) 0.9 mg kg^{-1}, over 1 h, with 10% of the dose given as an initial bolus. The maximum dose is 90 mg, which means that individuals with a weight above 100 kg will receive a lower dose per kg body weight. The effect of other doses of alteplase has not yet been evaluated in randomized controlled trials.

Intravenous thrombolysis: widening indications and restricting contraindications

As alteplase was originally licensed in Europe, accumulating scientific evidence has demonstrated that subgroups of patients who do not meet licensing criteria can nevertheless benefit from thrombolysis. For example, thrombolysis may be effective in patients older than 80 years of age for whom alteplase was not originally approved. Several studies reported in 2010 have suggested a benefit of thrombolysis above the age of 80 [64–67], and this benefit was confirmed by the third International Stroke Trial (IST-3) in 2012 [42].

Within the original licence, alteplase was not recommended for patients with the combination of previous stroke and diabetes and with ongoing anticoagulant treatment. Recent studies indicate that the treatment is safe for patients with previous stroke and diabetes [68] as well as for patients taking warfarin if the international normalized ratio (INR) value is below 1.7 [69].

Another example is the recommendation that patients with very severe stroke, that is those with a National Institutes of Health Stroke Scale (NIHSS) score of ≥25, should not be treated. An NIHSS score of 0 indicates that patients have no neurological deficit, and a higher score signifies a higher stroke severity. So far, the evidence is inconclusive, but subgroup analyses of randomized trials suggest treatment benefit for patients with severe stroke [42, 70].

Patients with very mild symptoms and those who recover significantly before initiation of thrombolysis may not need treatment, although there is no lower limit on the NIHSS for treatment. A treatment decision in these cases should be based on the clinical importance of the symptoms and information from neuroimaging [71]. For example, isolated dysphasia, contributing only one or two points on the NIHSS, may be a clinically significant deficit prompting treatment; another example is isolated haemianopia (frequently due to posterior cerebral artery occlusion) [72].

Seizure at the onset of stroke used to be considered a contraindication for thrombolytic treatment. Currently, a seizure is not a contraindication for thrombolysis if the neurological deficit is likely to be caused by cerebral ischaemia, for example in

Table 3 *Treatment indications and contraindications for intravenous thrombolysis*

Indications
Clinical diagnosis of ischaemic stroke
Age ≥ 18 years
Time from stroke onset ≤ 4.5 h
Absence of haemorrhage on admission CT scan
Contraindications
Hypersensitivity to rtPA or to any of the medication compounds
Severe stroke as assessed clinically (e.g. NIHSS score > 25 for anterior circulation stroke) and/or extensive early ischaemic changes on admission CT scan (defined as more than one-third of the MCA territory or half of other territories)
Other thrombolytic treatment within the previous 72 h
Known platelet count below 100 000 mm^{-3}
Clinically significant hypoglycaemia
Uncontrollable hypertension (blood pressure exceeding 185/110 mmHg at least twice within a 10-min interval) or aggressive management (at the discretion of the investigator, usually implying intravenous pharmacotherapy) necessary to reduce blood pressure to these limits
Current use of oral anticoagulants and a prolonged prothrombin time (INR > 1.7) or intake of direct oral anticoagulants with APTT above normal limits or within the latest 4 h[a]
Use of glycoprotein IIb/IIIa inhibitors within the past 72 h
Clinical suspicion of subarachnoid haemorrhage (even if CT scan is normal)
Use of heparin in previous 48 h, if APTT exceeds the laboratory upper limit of normal
Recent history of central nervous system damage (intracranial haemorrhage, neoplasm, ruptured aneurysm, intracranial or spinal surgery)
Active bleeding or acute trauma on examination, or recent severe bleeding
Known haemorrhagic diathesis/bleeding disorder
Recent (less than 10 days) traumatic external heart massage, obstetrical delivery or puncture of a noncompressible blood vessel (e.g. subclavian or jugular vein puncture)
Major surgery within the preceding 14 days, which poses a risk in the opinion of the investigator
Documented ulcerative gastrointestinal disease during the last 3 months, oesophageal varices, arterial aneurysm, arterial/venous malformations
Seizure at onset of stroke only if there is clinical suspicion of postictal residual neurological impairment which mimics stroke
Any condition that may be associated with an increased bleeding or other risk to the patient if intravenous thrombolysis is initiated (e.g. severe microangiopathy such as haemolytic uraemic syndrome or thrombotic thrombocytopenic purpura), at the discretion of the treating physician.

MCA, middle cerebral artery; CT, computed tomography; rtPA, recombinant tissue-type plasminogen activator; NIHSS, National Institutes of Health Stroke Scale; MCA, middle cerebral artery; INR, international normalized ratio; APTT, activated partial thromboplastin time.
[a]This is a preliminary recommendation because of limited experience to date and because the APTT is not completely reliable as a measure of the effect of direct oral anticoagulants.

patients with proven relevant arterial occlusion [73].

Patients with signs of extensive early infarction (i.e. clear hypodensity) on CT or MRI should be excluded but not those with early ischaemic changes [39, 74]. Usually, an 'extensive' infarct sign is defined as hypodensity of more than one-third of the middle cerebral artery territory, or half of the anterior or posterior artery territories.

Patients with a significant risk of haemorrhagic complications should also be excluded from thrombolytic treatment, such as those receiving ongoing oral warfarin treatment if the INR value is above 1.7 [69]. Similarly, the use of new oral anticoagulants or heparin within the previous 48 h is an exclusion criterion if the activated partial thromboplastin time (APTT) is not within the normal range. Furthermore, patients with a recent history of intracranial haemorrhage should be excluded from treatment, as should patients who have undergone major surgery within 2 weeks or experienced recent gastrointestinal or urinary tract bleeding or any condition (e.g. haemolytic uraemic syndrome or thrombotic thrombocytopenic purpura)

that could be associated with an increased bleeding or other risk to the patient according to the treating physician. Scores to evaluate the risk of haemorrhagic complications following thrombolysis have been published [75–78].

Blood pressure above 185/110 mmHg is a contraindication, but it is acceptable to treat patients with thrombolytic agents if blood pressure is first lowered below this level (see below for discussion of blood pressure management).

The importance of avoiding delays in management – time is brain

Although a net benefit of thrombolysis is proven within 4.5 h after stroke onset, the efficacy declines with longer time from symptom onset to treatment. In Fig. 4, the relation between onset-to-treatment time and full recovery after stroke is shown from an updated pooled analysis of randomized trials of stroke thrombolysis [10]. A good outcome is most likely in the early phase and decreases with time. Beyond 4.5 h, the benefit of intravenous thrombolysis is no longer statistically significant. The numbers needed to treat to achieve an excellent outcome [i.e. full functional recovery (mRS score 0–1) within 3 months] in one more patient are as follows: five, if treated within 90 min of stroke onset; nine, if treated between 91 and 180 min; and 15, if treated between 181 and 270 min [10]. Consequently, it is crucial to shorten the time from stroke onset to treatment [10].

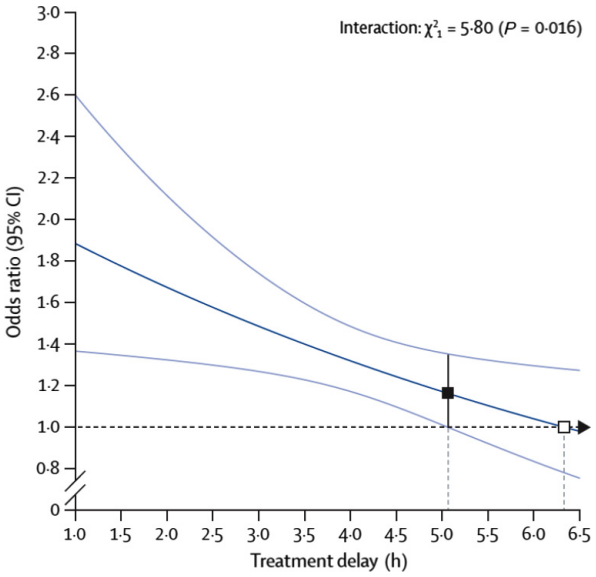

Fig. 4 *Effect of timing of alteplase treatment on good stroke outcome (mRS 0–1). The dark solid line is the best linear fit between the log odds ratio for good stroke outcome for patients given alteplase compared to control, and the light solid lines represent the 95% confidence limits. Estimates are derived from a regression model with alteplase, time to treatment, age and stroke severity included as main effects. The only treatment interaction included is with time to treatment. Adapted from Emberson* et al. *[43], with permission.*

Patients with an acute stroke onset should be transported to hospital with high priority and urgently evaluated by a stroke neurologist or physician. A CT or MRI scan should be performed immediately and, if the diagnosis of ischaemic stroke is confirmed and no contraindications are found, thrombolysis treatment should be initiated without delay. Preferably, the ambulance staff and the stroke physician should have communicated already during transport to enable the fastest possible management at arrival. After the treatment indication has been confirmed by a noncontrast CT or MRI scan, treatment should be initiated as soon as practically possible, even at the CT examination table. Additional diagnostic procedures, which would not influence the decision to treat, should be performed after initiation of treatment. Indeed, treatment can be initiated before laboratory test reports have been received if no specific disorders are suspected. Blood pressure exceeding 185/110 mmHg should be treated with intravenous antihypertensive agents to bring it below this level before thrombolytic infusion is started. There are currently several initiatives to accelerate the implementation of streamlined management. Campaigns to increase public knowledge of how to identify a stroke and how to urgently request an ambulance also aim to avoid delays from stroke onset to treatment.

Treatment risk: what is a symptomatic intracerebral haemorrhage?

Symptomatic intracerebral haemorrhage (SICH) is the main safety concern associated with thrombolysis and thrombectomy. The incidence of SICH depends on how it is defined. The most conservative definitions, the SITS-MOST [39] and the ECASS III definitions [12], are highly specific for haemorrhages occurring after thrombolysis. In recombinant tPA-treated patients in ECASS III, the rates of SICH were 1.9% and 2.4% with these definitions, respectively, compared to 0.2% for both

definitions in the placebo-treated control group [12].

The definition of SICH according to SITS-MOST is a local or remote parenchymal haematoma type 2 on the imaging scan obtained 22 to 36 h after treatment, plus neurological deterioration, as indicated by a score on the NIHSS that is higher by at least four points compared to the baseline value or the lowest value between baseline and 24 h, or haemorrhage leading to death [39]. Parenchymal haematoma (PH) adjacent to the infarct, termed local PH, was classified in the ECASS [12, 34] and SITS-MOST [39] as PH1 if blood clots did not exceed 30% of the infarcted area and had only a slight space-occupying effect, and as PH2 if blood clots were larger than 30% with a substantial space-occupying effect. A remote PH (PHr) is separated from the infarct (single or multiple) and is seen after thrombolysis without any visible infarct. PHr1 was defined as small or medium-sized blood clots located remote from the actual infarct with a mild space-occupying effect, and PHr2 as large confluent dense blood clots in an area remote from the actual infarct with substantial space-occupying effect [79].

The definition of SICH according to ECASS III is any haemorrhage with neurological deterioration, as indicated by an NIHSS score that is higher by at least four points compared to the value at baseline or the lowest value in the first 7 days, or any haemorrhage leading to death. Of importance, the haemorrhage must also have been identified as the predominant cause of the neurological deterioration [12].

Other definitions of SICH include those of ECASS II and the National Institute of Neurological Disorders and Stroke. Both these definitions are less specific for haemorrhages following thrombolysis than those of SITS-MOST and the ECASS III, as they also identify SICH in the control groups without thrombolysis treatment. The incidence of SICH is higher with the ECASS II (5.3% in active vs. 2.2% in control) and NINDS definitions (7.9% in active and 3.5% in control), compared with the incidence of SICH in the SITS-MOST (1.9% in active and 0.2% in control) and ECASS III definitions (2.4% in active and 0.2% in control [12].

The ECASS III and the SITS-MOST definitions are the preferred measures of SICH for future studies and for registries. The SITS-MOST definition is least dependent on variations in experience between local investigators and would be most suitable for large registries such as SITS-ISTR. In clinical trials with central reading of imaging data, the ECASS III definition would also be suitable.

Reducing the risk of haemorrhage: control of blood pressure before and after initiation of intravenous thrombolysis

There is limited knowledge of how to reduce the risk of haemorrhagic complications following thrombolysis. Avoiding treatment of patients with very high blood pressure is thought to reduce the risk. Risk scales based on known predictors of SICH may help to exclude patients at high risk of haemorrhage, although any decision to exclude a patient from treatment must be balanced against the potential benefit.

Thrombolysis is contraindicated if the blood pressure before treatment exceeds 185/110 mmHg because of the risk of intracerebral haemorrhage [60]. Attempts should be made to reduce blood pressure below these levels. Intravenous treatment with labetalol is frequently used for this purpose. A dose of 10–20 mg intravenous labetalol can be repeated, and it is normally advisable to refrain from thrombolysis if this does not result in sufficient lowering of blood pressure. In some countries, intravenous bolus and/or continuous infusion of urapidil is the preferred treatment for elevated blood pressure. Of note, blood pressure management differs in patients not receiving thrombolysis [15].

Blood pressure should be monitored during and after treatment: every 15 min during the first 2 h, every 30 min for the following 6 h and then hourly until 24 h after treatment initiation. If continuous infusion of an antihypertensive is used, blood pressure should be monitored at closer time intervals than 15 min (i.e. 5 min). Blood pressure should be kept below 180/105 mmHg. The ASA/AHA guidelines [15] for blood pressure control before, during and after initiation of intravenous thrombolysis or another acute reperfusion intervention are shown in Table 4. The levels to which blood pressure should be treated after initiation of thrombolysis are unclear, although an analysis from the SITS registry indicates a strong correlation between high systolic blood pressure and SICH, mortality and failure to reach functional independence at follow-up [80].

Table 4 *Approaches to arterial hypertension in patients with acute ischaemic stroke who are candidates for acute reperfusion therapy*

Patient otherwise eligible for acute reperfusion therapy except that BP is >185/110 mmHg:
Labetalol 10–20 mg IV over 1–2 min, may repeat 1 time; or nicardipine 5 mg h^{-1} IV, titrate up by 2.5 mg h^{-1} every 5–15 min, maximum 15 mg h^{-1}; when desired BP reached, adjust to maintain proper BP limits; or other agents (hydralazine, enalaprilat, etc.) may be considered when appropriate
If BP is not maintained at or below 185/110 mmHg, do not administer rtPA
Management of BP during and after rtPA or other acute reperfusion therapy to maintain BP at or below 180/105 mmHg:
Monitor BP every 15 min for 2 h from the start of rtPA therapy, then every 30 min for 6 h, and then every hour for 16 h
If systolic BP >180–230 mmHg or diastolic BP >105–120 mmHg
Labetalol 10 mg IV followed by continuous IV infusion 2–8 mg/min; or
Nicardipine 5 mg h^{-1} IV, titrate up to desired effect by 2.5 mg h^{-1} every 5–15 min, maximum 15 mg h^{-1}
If BP not controlled or diastolic BP >140 mmHg, consider IV sodium nitroprusside

BP, blood pressure; IV, intravenously; rtPA, recombinant tissue-type plasminogen activator.
From the American Heart Association/American Stroke Association 2013 guidelines for the management of acute ischaemic stroke [15].

Table 5 *Scoring model based on multivariable analysis of risk factors for symptomatic intracerebral haemorrhage (SICH) according to the Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS-MOST) after stratification for continuous variables*

Risk factor	OR (95% CI)	*P* value	Points
Aspirin + clopidogrel	3.2 (1.9–5.2)	<0.001	3
Aspirin monotherapy	1.8 (1.5–2.1)	<0.001	2
NIHSS ≥ 13	2.2 (1.7–3.0)	<0.001	2
NIHSS 7–12	1.6 (1.1–2.1)	0.006	1
Age ≥ 72 years	1.7 (1.4–2.0)	<0.001	1
Systolic BP ≥ 146 mmHg	1.6 (1.3–2.0)	<0.001	1
Weight ≥ 95 kg	1.6 (1.2–2.0)	<0.001	1
Onset-to-treatment time ≥ 180 min	1.5 (1.2–2.0)	0.002	1
History of hypertension	1.4 (1.1–1.7)	0.004	1

Overall risk level	Total score (points)	SICH rate, % (95% CI)
Low	0–2	0.4 (0.2–0.6)
Average	3–5	1.5 (1.3–1.7)
Moderate	6–8	3.6 (3.1–4.1)
High	≥9	9.2 (5.9–12.5)

NIHSS, National Institutes of Health Stroke Scale; BP, blood pressure; OR, odds ratio; CI, confidence interval.
Multivariate odds ratios with 95% confidence intervals. For clinical practicality, the total score is classified into four levels according to risk severity. Points are attributed strictly for either 'aspirin combined with clopidogrel' or 'aspirin as antiplatelet monotherapy'.
Lack of aspirin treatment and history of hypertension, NIHSS 0–6 and values of continuous parameters below the stated cut-off points are scored as 0 points. From Ref. [77].

Reducing the risk of haemorrhage: risk prediction scales

Several baseline factors independently predict the risk of haemorrhage following thrombolysis treatment [60]. Knowledge of these factors has stimulated the development of scales to identify patients with an increased risk of SICH [77, 78]. These scales may be used to help in the evaluation of an individual's risk/benefit balance for treatment with thrombolysis. Table 5 illustrates how the risk level can be predicted using the SITS SICH risk scale.

Management of suspected haemorrhagic complications

Haemorrhagic complications requiring treatment rarely occur during the infusion of alteplase (1-h duration). If the patient develops severe headache, lowering of the level of consciousness, nausea or vomiting during this period, the infusion should be stopped and an immediate CT scan requested.

There is no strong evidence for the treatment of SICH after thrombolysis with alteplase. The AHA/ASA guidelines recommend the infusion of platelets (6–8 U) and cryoprecipitate that contains factor VIII to rapidly correct the systemic fibrinolytic state created by tPA [15]. According to these guidelines, the recommendations for surgical treatment of intracerebral haemorrhage after thrombolysis for acute ischaemic stroke are the same as for intracerebral haemorrhage in general, but should be

initiated only after sufficient infusion of platelets and cryoprecipitate has stabilized the intracranial bleeding. Detailed recommendations for the management of intracerebral haemorrhage have also been published by the ESO [81]. The outcome of SICH is usually poor [82]. The level of evidence used to support recommendations has been systematically graded by the AHA/ASA and ESO.

Endovascular treatment of cerebral artery occlusion

In recent years, the development of diagnostic imaging has enabled rapid localization of cerebral artery occlusions and determination of their impact on cerebral perfusion and tissue integrity. In addition, imaging data can help to predict the effect of thrombolytic treatment. The findings from some studies suggest that thromboembolic occlusions of ≥6–8 mm are difficult to dissolve with intravenous treatment [83]. Other results suggest that recanalization after intravenous thrombolysis is poorer in larger arteries probably due to larger clot volumes [84, 85]. Therefore, additional procedures such as mechanical thrombectomy are needed.

The AHA/ASA guidelines from 2013 [15] stated: 'The MERCI, Penumbra System, Solitaire FR, and TREVO thrombectomy devices can be useful in achieving recanalization alone or in combination with pharmacological thrombolysis in carefully selected patients. Their relative effectiveness has not yet been established' (Class IIa, Level of Evidence B) and 'when mechanical thrombectomy is pursued, stent retrievers such as Solitaire FR and TREVO are generally preferred to coil retrievers such as MERCI (Class I, Level of Evidence A)' (Fig. 5). This statement was supported by trials of Solitaire and TREVO [49, 50, 86].

In February 2013, three randomized trials of endovascular treatment (SYNTHESIS, IMS 3 and MR Rescue) were published in the *New England Journal of Medicine* [46, 47, 87]. None of the studies demonstrated a benefit of such treatment compared to established routine practice. The results from these studies have been widely debated and referred to as evidence against the use of mechanical thrombectomy in the clinic. However, these trials have several important limitations. First, all were initiated several years ago (i.e. between 2004 and 2008). Secondly, the recruitment was very slow and the IMS 3 trial was stopped after inclusion of 600 of the initially planned 900 patients. Thirdly, CT angiography was not performed at randomization to verify a blood clot in two of the studies. Fourthly, many of the included patients (over half of those in SYNTHESIS and almost half in IMS 3) were not treated with mechanical thrombectomy but with intra-arterial pharmacological thrombolysis. Fifthly, because only 34% of treatments in the active arm included a device, the SYNTHESIS trial to a large extent compared immediate intravenous thrombolysis (control arm) with 1-h delayed intra-arterial thrombolysis (active arm). Because of the effects on outcome of substantially delaying treatment, it is understandable that the active arm did not provide an advantage over control. Finally, older mechanical devices such as MERCI and Penumbra were

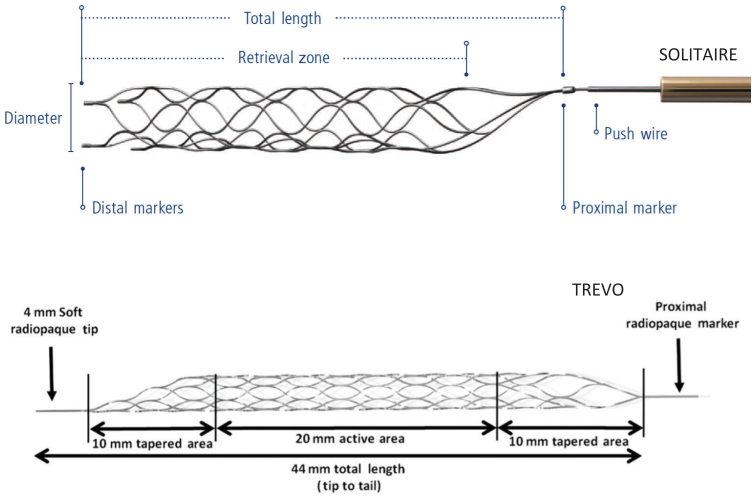

Fig. 5 *Two devices for mechanical thrombectomy, so-called stent retrievers. The stents are expanded within the thrombus, kept there for a short period, and then, the device with the blood clot is retrieved.*

used almost exclusively in these trials to treat patients. These studies therefore provided very limited information about mechanical thrombectomy using stent retrievers, which are almost exclusively used today.

Newer evidence for mechanical thrombectomy using stent retrievers

The use of a number of newer thrombectomy devices, that is stent retrievers, has been reported in the treatment of vessel occlusion in acute ischaemic stroke (Fig. 5). Successful recanalization was achieved in the clinical setting in 90% of patients with the Solitaire device, and the recanalization rate varied from 67% to 100% in a systematic review of 13 studies [88]. When the Solitaire device was applied as part of a stroke management protocol, including thrombectomy as rescue treatment, combined with thrombolysis or stand-alone treatment with selection of eligible patients by strict neuroimaging criteria (MRI ASPECT score < 5), the achieved recanalization rate was 84%, functional independence (mRS score 0–2) at 3 months 54% and mortality only 12% [89]. In a large single-centre study of the TREVO device, in which about 50% of patients were unsuccessfully treated with intravenous thrombolysis, recanalization was achieved in 73% of those who were treated with the TREVO device alone, and in 87–93% of patients when additional devices or intra-arterial tPA were used [90]. Good functional outcome in this study was reported in 45% of cases, and the mortality rate was 28%. Recently, in a study of the TREVO device, Jansen *et al.* [86] demonstrated 55% functional independence (mRS score 0–2) in patients mostly with occlusions of the proximal middle cerebral artery and terminal carotid artery, and a median baseline stroke severity of 17 on the NIHSS. Both the Solitaire and TREVO devices (Fig. 5) demonstrated a favourable outcome compared to the older MERCI device [49, 50].

Between January and April 2015, five randomized controlled trials reported overwhelming support for mechanical thrombectomy using stent retrievers: MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME and REVASCAT (Table 6) [16–20]. All of these trials reported positive outcomes for their primary endpoints. Stent retrievers were the dominating method. Most patients received intravenous thrombolysis within 4.5 h. The treatment time window for starting intervention was 6 h, except for in REVASCAT (8 h) and ESCAPE, which accepted 12 h. All trials included functional outcome on the mRS as primary or secondary end-points. There was an absolute increase in the proportion of patients with functional independence, corresponding to a score of 0–2 on the mRS between 13% and 31%. As a comparison, the improvement in the rate of disability-free survival (mRS score 0–1) is 10% for intravenous thrombolysis treatment within 3 h of the stroke, and 5% for those treated between 3 and 4.5 h after the event [43].

Based on a consensus group discussion at the ESO-Karolinska Stroke Update conference in Stockholm in November 2014, and its final statement in February 2015, the professional organizations, The European Stroke Organisation (ESO), the European Society of Minimally Invasive Neurological Therapy (ESMINT) and the European Society of Neuroradiology (ESNR), issued new recommendations on mechanical thrombectomy, including that: 'Mechanical thrombectomy, in addition to intravenous thrombolysis within 4.5 hours, when eligible, is recommended to treat acute stroke patients with large artery occlusions in the anterior circulation up to 6 hours after symptom onset' [81].

The bridging approach

A general concern when conducting thrombectomy studies is that the advantage of higher rates of recanalization with thrombectomy is weakened by a longer time delay to treatment initiation compared to intravenous thrombolysis [91, 92]. To avoid the problem of time delay and maintain a good chance of final successful recanalization, a combination, or 'bridging', of intravenous thrombolysis and endovascular treatment was proposed. This approach was first tested in 1999 in a randomized trial of combined intravenous thrombolysis and local intra-arterial recombinant tPA therapy for stroke within 3 h of onset of symptoms versus standard intravenous thrombolysis alone [93]. Bridging treatment was investigated in the above-mentioned IMS 3 trial [46]. In a recent meta-analysis, pooled estimates associated with bridging therapy of any kind were 69.6% for recanalization rates, 48.9% for favourable outcome, 17.9% for mortality and 8.6% for SICH [94], thus supporting the safety and efficacy of a bridging approach in patients with stroke.

The advantage of a combined intravenous thrombolysis and thrombectomy approach was demonstrated by a prospective registry-based study of patients with confirmed arterial occlusion:

Table 6 *Randomized trials of endovascular treatment*

Name of trial	No. of pts	Type of intervention	Control group	Time window (h)	Primary end-point	Absolute difference intervention–control for independence at 90 days (mRS 0–2)
MR CLEAN	500	Endovascular treatment (stent retrievers 81.5%) plus usual care (87.1% IVT)	Usual care (90.6% IVT)	0–6	mRS at 90 days (mRS 0–2)	13.5% (95% CI 5.9–21.2)
ESCAPE	316	Endovascular treatment (stent retrievers 86.1%) plus standard care (72.7% IVT)	Standard care (78.7% IVT)	0–12	mRS at 90 days (OR for 1 point improvement in mRS)	23.8% (95% CI 17.8–39.2)
EXTEND-IA	70	Endovascular thrombectomy (Solitaire FR stent retriever) plus IVT <4.5 h	IVT <4.5 h	0–6	Reperfusion 24 h Early neurological improvement	31% ($P = 0.01$)
SWIFT PRIME	196	Endovascular thrombectomy (Solitaire FR stent retriever) plus IVT <4.5 h	IVT <4.5 h	0–6	mRS shift at 90 days	24.7% ($P < 0.001$)
REVASCAT	206	Endovascular thrombectomy (Solitaire FR stent retriever) plus usual care (77% IVT)	IVT <4.5 h	0–8	mRS shift at 90 days	15.5% (adjusted OR 2.1; 95% CI 1.1–4.0)

pts, patients; mRS, modified Rankin Scale; IVT, intravenous thrombolysis; CI, confidence interval; FR, flow restoration; OR, odds ratio.

successful recanalization was achieved in 87% of patients treated with the combination treatment [95]. However, most of the data regarding thrombectomy after failed intravenous thrombolysis are from small observational studies (or from subgroups of subjects in larger studies) [91, 95, 96], and have been criticized because such studies lacked control arms and included potential selection bias (towards treating patients more likely to be recanalized) or the primary end-points were procedural (e.g. recanalization) rather than clinical (e.g. mRS scores at 3 months).

Findings have suggested that intravenous thrombolysis, even if not effective, enhances the efficacy of subsequent mechanical revascularization [95, 96]; however, these observations were not tested in a study with a control arm. Based on SITS registry data, Kharitonova *et al.* have demonstrated the effect of large cerebral artery occlusions as indicated by hyperdense middle cerebral artery sign (HMCAS) on CT scans [97, 98]. About 50% of the HMCAS disappeared after intravenous thrombolysis when re-examined between 22 and 36 h after treatment initiation. The rate of independence (mRS score 0–2) at 3 months was 41.5% for patients in whom HMCAS disappeared, but was only 19.0% for those in whom the sign persisted [98]. These findings indicate that some large occlusions are insufficiently resolved by intravenous thrombolysis, and an additional approach to achieve recanalization could be expected to improve the prognosis.

Final evidence of the safety and efficacy of the bridging concept emerged from the five randomized controlled trials of mechanical thrombectomy published early in 2015 (Table 6) [16–20].

Mechanical thrombectomy: today and in the future

Considering the new evidence from these randomized controlled trials, establishing services for highly specialized stroke treatments will be a

challenge in the next few years. As mechanical thrombectomy is most likely to be concentrated in regional centres, it will be necessary to establish methods to identify potential thrombectomy patients whilst still in the ambulance.

Recently, a SITS registry study found that NIHSS scores of 11 and 12 points predicted baseline vessel occlusion and functional independence at 3 months in a cohort of 11 632 patients with available baseline imaging and 3-month functional outcome data. If imaging was performed 3 h after stroke onset, NIHSS score thresholds decreased to 9 and 10 points to predict baseline vessel occlusion and functional outcome at 3 months, respectively [99]. Similar results were found in a single-centre retrospective study of 162 patients [100].

Such evidence may be used for the development of triage methods to admit patients to regional stroke centres with capacity to perform mechanical thrombectomy.

Enhanced intravenous thrombolysis in acute ischaemic stroke

Interventional stroke treatment has some inherent limitations such as limited availability of skilled interventionists and of angiography equipment. In addition, the cost of treatment (i.e. mechanical retrievers) is high. Moreover, interventional treatment increases the time delay to initiation of the procedure. Therefore, approaches to recanalize brain arteries more quickly, easily, safely and cheaply (compared to current standards or interventional treatment) are required.

Several such strategies have been tested, including combination of a thrombolytic agent with aspirin [101], an anticoagulant (argatroban) [102, 103] or a glycoprotein IIb/IIIa antagonist (eptifibatide) [104], combination of a thrombolytic agent with sonothrombolysis [52], the use of a new generation of thrombolytic agents such as tenecteplase [105] or lowering the dosage of alteplase. To date, only one Phase III trial has been completed, showing that early combined administration of intravenous aspirin and alteplase does not improve outcome but rather increases haemorrhagic complications [101]. A Phase III trial of the combination of alteplase and transcranial ultrasound (CLOTBUST-ER) designed to evaluate clinical benefit compared to alteplase alone was stopped in April 2015 due to futility. The CLOTBUST-ER trial was based on a previous Phase II trial (CLOTBUST) which showed an improved recanalization rate if alteplase was combined with continuous transcranial ultrasound monitoring as compared to alteplase alone [52]. Different mechanisms of action of ultrasound have been considered including better penetration of thrombolytic agents into the clot due to induction of 'microstreaming' in the residual flow around the thrombus or improvement of the microcirculation leading to decreased infarct volume [106].

Data regarding the combinations of anticoagulants [102, 103, 107] or glycoprotein IIb/IIIa [104] antagonists are promising, but definitive evidence of their efficacy has not been provided.

The aim of the above-mentioned trials is to increase the efficacy of stroke treatment. An alternative approach could be to improve the safety of intravenous recombinant tPA treatment by decreasing dosage. Currently, a dose of 0.9 mg kg^{-1} alteplase is the recommended dose in most parts of the world [15, 61, 62]. However, data from Asia, especially Japan, support the use of 0.6 mg kg^{-1} [108]. Other data showed that alterations of dosing in clinical practice, especially due to incorrect body weight estimation, do not affect efficacy or safety [109, 110]. The ongoing Phase III Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED) will compare the effects of 0.6 and 0.9 mg kg^{-1} alteplase [111].

Prevention of early stroke recurrence

Patients with acute ischaemic stroke are usually started on antiplatelet agents directly after admission to hospital as long as a cerebral haemorrhage and cardioembolic cause has been excluded. For those not excluded and treated with intravenous thrombolysis, antiplatelet treatment is delayed by 24 h. In the early acute phase of ischaemic stroke, there is evidence of the benefit of medium-dose aspirin but not in the very early phase of other antiplatelet agents (clopidogrel or dipyridamole) [23, 24]. Therefore, medium-dose aspirin (different dosages are available in different countries) is recommended in the acute phase [15]. Moreover, there is evidence for the benefit of dual antiplatelet therapy started within 24 h from symptom onset in patients with minor ischaemic stroke (defined as an NIHSS score of <4) or high-risk TIA (defined as an ABCD2 score of ≥4 [112, 113]; the acronym stands for age, blood pressure, clinical features, duration of TIA and diabetes): in the CHANCE trial,

dual antiplatelet therapy with clopidogrel and aspirin (clopidogrel at an initial dose of 300 mg, followed by 75 mg per day for 90 days, plus aspirin at a dose of 75 mg per day for the first 21 days) was superior to aspirin alone [25]. For secondary prevention after the acute phase, other recommendations apply [114].

Treatment of SICH

The optimal treatment of SICH still needs to be determined. Recombinant factor VII reduces haematoma growth but does not improve functional outcome [115, 116]. Another potential strategy to limit haematoma growth is to lower blood pressure. In the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial-2 (INTERACT-2), patients with elevated systolic blood pressure treated intensively (with a target systolic blood pressure level of <140 mmHg within 1 h) were compared with those treated according to standard practice (with a target systolic blood pressure level of <180 mmHg). Ordinal analysis of mRS scores showed improved functional outcomes with intensive lowering of blood pressure [117]. Therefore, blood pressure lowering is a promising treatment for intracerebral haematoma, but this approach needs to be confirmed in further studies.

Evacuation of haematomas, especially in deep locations (basal ganglia or thalamus), does not improve outcome [118]. However, patients with spontaneous superficial intracerebral haemorrhage might obtain some benefit [118]. More studies of the effect of haematoma evacuation are ongoing.

Summary

Stroke is a devastating disease. Intravenous thrombolysis is currently the only evidence-based treatment that can reverse neurological deficit, but this therapy is still underused. Moreover, in many countries, the logistical management required for thrombolysis use is insufficiently developed. The times from stroke onset to calling an ambulance, to arrival at hospital and to initiation of treatment are still unacceptably long, even the delay with hospitals. The median delay from hospital arrival to treatment is about 60 min in large observational studies [39, 119], although many centres are currently improving their routines. Because these delays depend on public awareness, as well as prehospital and in-hospital management, increased information for the public, education of ambulance teams and improved acute management at hospitals should result in more patients being treated and attaining functional recovery. Additional approaches, such as endovascular intervention and sonothrombolysis, may further improve the outcome for patients with acute ischaemic stroke. This is a challenge that requires the attention of all healthcare professionals involved in acute stroke management.

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