ELSEVIER
SAUNDERS

Neurol Clin 26 (2008) 943–961

NEUROLOGIC
CLINICS

Acute Ischemic Stroke Management: Administration of Thrombolytics, Neuroprotectants, and General Principles of Medical Management

Aslam M. Khaja, MD

Department of Neurology and Rehabilitation, University of Illinois at Chicago, 912 South Wood Street, MC 796, Chicago, IL 60612, USA

Acute ischemic stroke (AIS) care has undergone a revolution since the approval of intravenous (IV) recombinant tissue plasminogen activator (rt-PA) for acute ischemic stroke by the US Food and Drug Administration (FDA) in 1995. Previously, ischemic stroke was a devastating disease with limited effective therapies. Although IV rt-PA remains the only approved therapy, numerous clinical trials are ongoing to expand treatment windows, increase the number of patients eligible for therapy, and evaluate new and innovative therapies, particularly for neuroprotection and intra-arterial (IA) reperfusion therapy.

Pathophysiology

In ischemic stroke, decreased or absent circulating blood flow deprives neurons of necessary metabolic substrates. Because the brain does not store glucose, ischemia is tolerated poorly [1]. Cerebral blood flow usually is compromised because of occlusion of a cerebral artery by a clot. The ischemic cascade begins with ATP depletion, which results in failure of the Na^+/K^+ pump. Subsequently, the activation of voltage-sensitive calcium channels results in calcium influx. The calcium influx results in glutamate release. Glutamate release leads to neuronal activation and further calcium influx, which perpetuates the ischemic cascade [2]. Calcium influx also activates intracellular enzymes, leading to further destruction of cell membranes.

E-mail address: aslam.m.khaja@uic.edu

doi:10.1016/j.ncl.2008.07.002

This process results in free radicals and nitrous oxide. All of these processes result in continued neuronal damage and cell death. The extent of damage depends upon various factors. Acute ischemia is not tolerated as well as progressive ischemia over time. The amount of collateral flow can influence the size of the infarct and ischemic penumbra. Temperature and glucose metabolism also have effects on cell death and tissue injury [3,4].

An important concept in AIS is the penumbra. When an artery occludes, neurons are affected differently, depending upon the amount of residual blood flow. Normal cerebral blood flow is greater than 50 mL/100 mg/min [1]. Once blood flow decreases to less than 20 mL/100 mg/min, infarction occurs. If blood flow decreases to less than 10 mL/100 mg/min, irreversible neuronal death occurs rapidly. Blood flow between 11 and 20 mL/100 mg/min is thought to represent the ischemic penumbra [5], an area where the cells are functionally silent because of ischemia, but are still able to recover if blood flow is restored. Many acute stroke therapies are targeted toward restoring flow or function to the ischemic penumbra.

Thrombolysis

The first method to restore cerebral perfusion is clot lysis, with the goal of re-establishing blood flow to the affected tissue. IV thrombolysis rt-PA is the only FDA- approved treatment for AIS. Endogenous tissue-plasminogen activator converts circulation plasminogen to plasmin, an enzyme responsible for fibrin dissolution and maintaining coagulation homeostasis. Fibrinolysis is enhanced powerfully by rt-PA. The pivotal United States trial was the National Institute for Neurologic Disorders and Stroke (NINDS) rt-PA Stroke Study. In this randomized, double-blind placebo-controlled trial, 624 patients received either rt-PA (0.9 mg/kg IV) or placebo. Favorable outcomes were reported in 31% to 50% of rt-PA-treated subjects, compared with 20% to 38% in the placebo group. Patient who received rt-PA were 30% more likely to have minimal or no disability at 3 months (odds ratio [OR] 1.7, 95% CI 1.2 to 2.6) [6]. As the major adverse affect is bleeding, only selected patients are eligible for thrombolysis; inclusion and exclusion criteria are listed in Box 1.

The treatment protocol for IV rt-PA administration is outlined in Box 2. The most serious complication of IV rt-PA treatment is symptomatic intracranial hemorrhage primarily from hemorrhagic transformation (HT) of the infarct. Factors associated with HT are increased blood pressure (BP), early ischemic changes on CT, and high National Institute of Health Stroke Scale (NIHSS) score [7]. In addition, increasing age and hyperglycemia may play a role [8]. The symptomatic intracranial hemorrhage rate in the NINDS trial was 6.4% [6]. The optimal methods to limit complications from HT are careful patient selection, scrupulous ancillary care, close monitoring, and strict adherence to BP limits [2]. There are no approved measures to control

Box 1. Criteria for thrombolysis with recombinant tissue plasminogen activator in acute ischemic stroke

Inclusion criteria
Clinical signs and symptoms consistent with ischemic stroke
Patient last seen normal within 3 hours
Measurable neurologic deficit
Exclusion criteria
Any hemorrhage on neuroimaging (CT or MRI)
Symptoms suggestive of subarachnoid hemorrhage
Seizure at stroke onset that is thought to contribute to neurologic deficit
Hypodensity greater than one third cerebral hemisphere on CT
Systolic blood pressure (SBP) greater than 185 mm Hg or diastolic blood pressure (DBP) greater than 110 mm Hg
Serum glucose less than 50 mg/dL
Platelet count less than 100 K/mm^3
International normalized ratio (INR) greater than 1.7
Elevated partial thromboplastin time (PTT)
Any history of intracranial hemorrhage
Arterial puncture at a noncompressible site in past 7 days
Major surgery in past 14 days
Gastrointestinal (GI) bleed or hematuria in past 21 days
Ischemic stroke, myocardial infarction, or serious head trauma in past 3 months

Adapted from Khaja AM, Grotta JC. Established treatments for acute ischaemic stroke. Lancet 2007;369(9558):323; with permission.

HT after IV rt-PA; published recommendations are 6 to 8 U of platelets and cryoprecipitate-containing factor 8 [9]. Carefully selecting patients for thrombolysis is critical, because deviations from criteria have been shown to increase the risk of adverse events [10–12]. These criteria only are intended to serve as a guide for selecting patients. Patients younger than 75 years of age and with mild-to-moderate strokes respond best to IV rt-PA [6].

Some controversy exists regarding the appropriate selection of patients. Most thrombolysis trials excluded patients over the age of 80, with the exception of the NINDS trial [13]. Although never fully studied in clinical trials, in clinical practice, IV rt-PA in the elderly has been reported safe without an increased risk of HT [14,15]. The outcome of elderly patients is generally worse than those younger, but this may be because of other comorbid conditions rather than age alone [16,17]. The effectiveness of thrombolysis in the elderly requires further examination, but the evidence does not support excluding patients based on age alone.

Box 2. Intravenous recombinant tissue plasminogen activator administration protocol.

Total dose of rt-PA: 0.9 mg/kg (maximum dose 90 mg)
Give 10% as initial IV bolus
Infuse remainder over 1 hour
Admit patient to an ICU or stroke unit for monitoring
Neurologic assessments: every 15 minutes during infusion, then every 30 minutes for next 6 hours, then every hour until 24 hours after treatment
BP monitoring: every 15 minutes for 2 hours, then every 30 minutes for next 6 hours, then every hour until 24 hours after treatment
Administer antihypertensive medication to maintain systolic BP less than or equal to180 mm Hg and diastolic BP less than or equal to 105 mm Hg
Delay placement of nasogastric tubes, indwelling bladder catheters, or IA pressure catheters
Follow-up CT or MRI scan at approximately 24 hours after rt-PA, before starting anticoagulation or antiplatelet agents
Delay antithrombotic agents for 24 hours after rt-PA

Data from Adams HP Jr, del Zoppo G, Alberts MJ, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Groups. Stroke 2007;38(5):1676; with permission.)

Another controversy concerns patients who have minor neurologic deficits or spontaneously improving symptoms. Minor deficits have been documented as justification to exclude up to 30% of otherwise rt-PA-eligible patients from receiving thrombolytic therapy [18]. Patients who have minor neurologic deficits, however, may not have favorable outcomes at discharge [19]. Treating patients who have mild neurologic deficits may improve their outcomes at discharge [20]. A similar controversy exists regarding patients with major neurologic deficits, who have a poor prognosis in general. Such patients have an increased chance of complete recovery after thrombolysis, but overall success remains low [6]. As mentioned previously, patients who have high NIHSS scores have an increased risk of HT [7]. The decision to treat or not treat in these patients is a carefully weighed clinical decision.

CT changes on initial neuroimaging are another controversy (Fig. 1). Early ischemic changes on initial CT are associated with more severe symptoms and a longer time from symptom onset [21]. Patients who have early

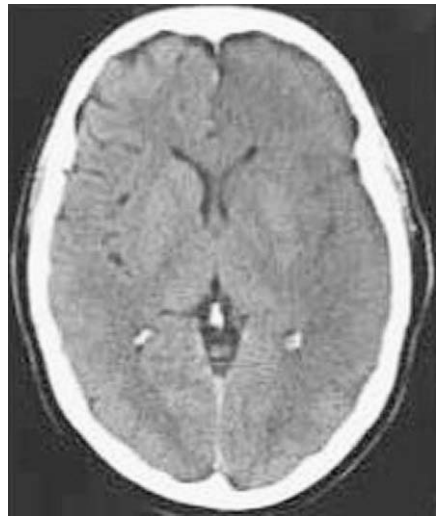

Fig. 1. Early ischemic changes on CT scan. Note the subtle loss of gray–white differentiation and sulcal effacement in the middle and anterior cerebral artery distributions on the left hemisphere.

signs of ischemia on head CT may be at increased risk of HT after IV rt-PA therapy [22,23]. Published studies, however, also report that patients who have early ischemic changes on CT should not be excluded from thrombolysis, and may have greater benefit from rt-PA [24]. Many risk factors for early ischemic CT changes, such as severe symptoms and longer duration of symptoms, also are associated with poorer outcomes [21]. The impact of early ischemic changes on CT scan on outcomes after thrombolysis remains unclear.

Another area of concern regarding thrombolytic therapy for AIS is consent. IV rt-PA is an FDA-approved therapy for AIS for patients meeting criteria. As with any medical intervention, a full discussion of risks and benefits of IV rt-PA treatment with the patient and/or legally authorized surrogate is recommended, if possible. Treatment should not be withheld, however, if the patient is incapable of decision-making, and the legally authorized surrogate is unavailable. Written consent is not necessary [2].

Emerging and experimental therapies

Numerous strategies are being evaluated for treating AIS. These include IA thrombolysis (IAT), augmentation of rt-PA with other medications, lengthening of the therapeutic window, and neuroprotection.

IAT may be a treatment option for selected patients. Possible selection criteria include presentation between 3 and 6 hours from symptom onset, major cerebral artery occlusion, severe neurologic deficits, and high risk

of systemic hemorrhage with IV rt-PA (eg, recent surgery). In most circumstances, the availability of IAT should not preclude the use of IV rt-PA in patients meeting criteria. IAT requires access to emergent cerebral angiography, experienced stroke physicians, and neurointerventionalists; it should be performed only at an experienced center [2].

The MERCI (Mechanical Embolus Removal in Cerebral Ischemia) retrieval system (Concentric Medical, Inc., Mountain View, California) has been FDA-approved for recanalizing acutely occluded cerebral arteries. In the Multi-MERCI study, patients who did not improve immediately after IV rt-PA underwent mechanical embolectomy within 8 hours of symptom onset. Partial or complete recanalization occurred in 74% of patients, with a symptomatic intracerebral hemorrhage (sICH) rate of 6.7% [25]. Mechanical embolectomy with the MERCI retriever may be a feasible and safe option for patients after IV rt-PA. Further research, however, is needed to assess the effect on clinical outcomes.

Another newer FDA approved device for AIS is the Penumbra stroke system (Penumbra, Inc., Alameda, California). This device combines two methods of clot extraction, aspiration and mechanical extraction. First the clot is aspirated; then a thrombus removal ring can be used if necessary to remove remaining clot. In 125 patients who had AIS, the Penumbra system was successful recanalizing 82% [26]. This study was not designed to assess clinical outcomes, and this needs to be addressed in future trials. Other recanalization devices also are being tested for improving cerebral artery recanalization rates (Fig. 2).

IV rt-PA followed by local IAT is known as bridging therapy. The Emergency Management of Stroke Bridging Trial showed that patients randomized to treatment with 0.6 mg/kg IV rt-PA followed by IAT with IA rt-PA (up to 20 mg) achieved a higher recanalization rate (54%) compared with those treated with IA rt-PA alone (10%) ($P = .03$) [27]. Bridging therapy also has been evaluated in the Interventional Management of Stroke (IMS) phase 1 and 2 trials. All patients received 0.6 mg/kg IV rt-PA followed by IA rt-PA. Partial or complete recanalization was achieved in 56% of patients. The risk of sICH (6.3%) was similar to patients treated with IV rt-PA in the NINDS trial. When this group of patients was compared with the placebo arm of the NINDS trial, the odds of a good outcome, defined as a modified Rankin scale of 0 to 2, was higher (OR 2.18, 95% CI 1.20 to 3.99) [28]. The IMS III trial is comparing 0.9 mg/kg IV rt-PA to 0.6 mg/kg IV rt-PA followed by IAT. IAT includes the MERCI retriever, EKOS ultrasound catheter (EKOS Corporation, Bothell, Washington), or local IA rt-PA. In other series, IAT after 0.9 mg/kg IV rt-PA has been reported to be safe and may achieve higher rates of recanalization compared with IV alone [29].

There are limited published data for emergent angioplasty and stenting of intracranial and extracranial vessels after AIS. IAT in conjunction with angioplasty and stenting for acute stroke may increase the chance of sustained

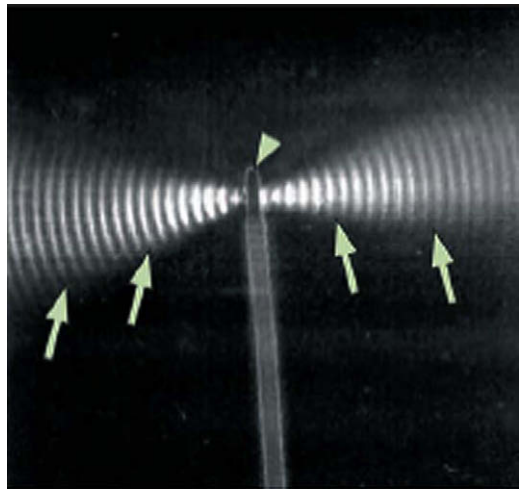

Fig. 2. EkoSonic SV Endovascular Device which uses intravascular ultrasound technology to enhance clot lysis. (*Courtesy of* EKOS Corporation, Bothell, Washington; with permission.)

recanalization and favorable outcome [30]. Endovascular interventions for AIS are a popular area of development, and hopefully will provide additional tools to aid patients in the future.

Adjunctive medications to complement the fibrinolytic action of rt-PA are being studied. Platelet aggregation is critical step for clot formation, and the final common step in platelet aggregation is the binding of fibrinogen between two platelets at the glycoprotein IIb/IIIa receptor. Glycoprotein IIb/IIIa inhibitors such as eptifibatide, abciximab, and tirofiban have garnered interest in AIS. Eptifibatide is being studied in conjunction with IV rt-PA treatment in the CLEAR trial (Combined approach to Lysis using Eptifibatide AND Rt-PA in acute ischemic stroke). Abciximab showed promise in phase 1 and 2 trials; however, a phase 3 trial was stopped early because of increased hemorrhage rates. Tirofiban is the newest member in this class, and has been studied in one phase 2 trial [31]. Further research is necessary before these agents can be recommended for treating AIS.

Argatroban, a direct thrombin inhibitor, combined with IV rt-PA, may improve clot dissolution and recanalization and decrease reocclusion rates. Early results of this paradigm suggest safety and potential efficacy [32].

Other thrombolytic agents continue to be developed and tested. Streptokinase use for AIS is not recommended because of high rates of intracerebral hemorrhage in previous trials [33]. Tenecteplase, a derivative of rt-PA, has a longer half-life and is more fibrin-specific than rt-PA and has been reported safe in a phase 2 study, with no cases of sICH in 88 treated patients who had AIS [34]. A phase 2b trial is underway to evaluate IV

tenecteplase versus IV rt-PA for patients who have AIS within 3 hours from symptom onset [35].

Fibrinogen-depleting agents, such as ancrod and batroxobin, may have a more favorable safety profile than thrombolytic drugs. A meta-analysis revealed a 10% relative risk reduction for death and disability in patients who had AIS treated with fibrinogen-depleting agents compared with thrombolytic treatment [36]. Ancrod, however, derived from pit viper venom, did not show clinical benefit in one trial when used within 6 hours of AIS, and additional studies are ongoing [37].

Despite favorable prepivotal studies, desmoteplase, derived from vampire bat saliva, failed to show efficacy in a large phase 3 study of AIS patients who had MRI diffusion–perfusion mismatch presenting between 3 and 9 hours from symptom onset [38]. The future of desmoteplase is uncertain.

Transcranial Doppler ultrasound (TCD) is a novel technique to enhance rt-PA activity. Possible mechanisms include improved drug transport and enhanced binding between rt-PA and fibrin [39]. In the CLOTBUST study (Combined Lysis of Thrombus in Brain Ischemia Using Transcranial Ultrasound and Systemic t-PA) patients who had AIS received IV rt-PA within 3 hours of symptom onset and were randomized to continuous 2 MHz TCD or sham TCD procedure. TCD significantly increased the chance of complete recanalization or dramatic clinical recovery, 49% compared with 30%, ($p = .03$). The study was not powered to show efficacy [40]. TCD may have adverse effects. Midrange TCD frequency (300 MHz) in conjunction with IV rt-PA has been associated with an increased risk of intracerebral hemorrhage [41]. Studies are underway to evaluate IV rt-PA, continuous TCD, and microbubbles in combination after AIS [35]. Ultrasound technology also is being used in IA catheters to enhance thrombolysis (see Fig. 2).

The most frequently cited reason for excluding patients from IV rt-PA is presentation outside the 3-hour window [18]. Most studies using IV rt-PA and other IV thrombolytics beyond 3 hours have failed to show a benefit. However, a pooled analysis of IV rt-PA studies showed a potential benefit of IV rt-PA up to 4.5 hours after symptom onset [42] (Fig. 3). Recently, a European study is the first to show a significant improvement in clinical outcomes when AIS patients were treated with IV rt-PA 3 to 4.5 hours after symptom onset. Furthermore, there was not an increased risk of hemorrhagic transformation when compared to other rt-PA studies, despite the longer time to treatment [43]. Studies of IV rt-PA within 6 hours of symptom onset are ongoing. A this time, routine use of IV rt-PA beyond 3 hours has not yet been recommended.

Because trials of IV thrombolysis beyond 3 hours have been largely unsuccessful, attention has been focused on better ways of selecting patients beyond 3 hours who might benefit from reperfusion therapies. Acute MRI scanning with diffusion-weighted-imaging (DWI) is capable of approximating infarct size, and perfusion-weighted-imaging (PWI) may provide information about the ischemic penumbra and tissue at risk when compared

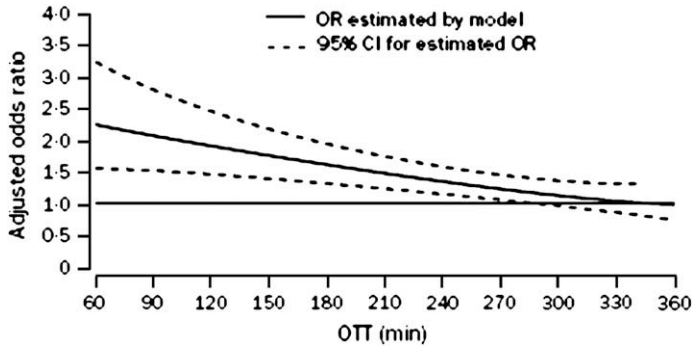

Fig. 3. Model estimating the odds ratio for a favorable outcome at 3 months in intravenous rt-PA treated patients compared with controls. Adjusted for age, baseline glucose, baseline National Institutes of Health (NIH) stroke scale score, baseline diastolic blood pressure, previous hypertension, and interaction between age and baseline NIH stroke scale score. (*From* Hacke W, Donnan G, Fieschi C, et al. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. Lancet 2004;363(9411):772; with permission.)

with the DWI lesion (ie, mismatch) [35]. The mismatch hypothesis was tested in the DEFUSE (Diffusion-weighted imaging Evolution for Understanding Stroke Etiology) study. In DEFUSE, patients presenting within 3 to 6 hours after stroke symptom onset received an MRI scan, and those who had ischemic stroke then were treated with IV rt-PA 0.9 mg/kg. The pretreatment MRI scans then were analyzed retrospectively to identify subgroups of patients who might have benefited from treatment. Early reperfusion on PWI occurred in 49% of patients treated with IV rt-PA. A favorable clinical response occurred in 45% of patients with early reperfusion, compared with 35% in patients without early reperfusion ($P = .55$). Patients without a mismatch were not observed to benefit. In addition, a malignant profile was identified. Patients who had a DWI or a PWI lesion volume of greater than 100 mL were at higher risk of severe intracranial hemorrhage and poor outcome [44]. Further research is needed to confirm if patients who have a mismatch can benefit from IV thrombolysis beyond the 3-hour window.

Although the absolute effect is small, aspirin has been shown in clinical trials to reduce death and disability when initiated within 48 hours of symptom onset [45,46]. More recently, clopidogrel loading with an initial 300 mg dose and then 75 mg/d has been shown to be effective for reducing myocardial infarction risk during acute coronary syndrome [47]. One small study evaluated a one-time loading dose of clopidogrel 375 mg and aspirin 325 mg within 36 hours of stroke onset in patients not eligible for thrombolysis. Patients receiving clopidogrel loading were less likely to suffer neurologic deterioration compared with patients who were not loaded, without an increased risk of hemorrhage [48].

Research in AIS therapy is following a course similar to that of acute coronary syndrome (ACS), with an increasing emphasis on multiple pharmacologic agents in combination with percutaneous intervention. The current approach in ACS is antiplatelet therapy with aspirin, clopidogrel, and glycoprotein IIb/IIIa inhibitors; antithrombotic therapy with heparin; and direct percutaneous coronary intervention. Because the brain may be less tolerant of ischemia and at greater risk for devastating intracerebral hemorrhage from reperfusion than the myocardium, novel approaches first should be thoroughly evaluated for safety.

Neuroprotection

The term neuroprotectant refers to medications and other therapies designed to interrupt the process of cellular death within the brain itself, not directed toward improving vascular flow. This includes many medications and other therapies such as hypothermia and magnesium. Neuroprotection trials have a poor history of success, but past failures may have been caused in part to trial design. Suboptimal dosages, uncertain durations of therapy, and lengthy time windows may have contributed to past failures in neuroprotection [49].

Magnesium functions as an N-methyl-D-aspartic acid (NMDA) receptor blocker and voltage-gated calcium channel blocker. Magnesium is widely available, crosses the blood–brain barrier easily, and generally is tolerated well. As there are few acute adverse effects of used doses, Magnesium is a hyperacute intervention, being tested by paramedic administration in the field to patients who have acute focal neurologic symptoms. Field administration of magnesium sulfate has been reported to be feasible and safe in acute stroke patients [50]. The dose being studied is a 4 mg load in the field, followed by 16 g over 24 hours in the hospital. Further study is needed, but hyperacute prehospital therapies for AIS similar to myocardial infarction are desirable.

Another novel neuroprotectant is a combination of caffeine and ethanol, known as caffeinol. Low doses, the equivalent of 2 to 3 cups of coffee and one cocktail, have reduced infarct volume is up to 83% in animal models. Caffeinol may be more beneficial in cortical tissue compared with white matter, based on animal studies. Additionally, animals pretreated with daily ethanol have a diminished caffeinol effect, but not those pretreated with daily caffeine [51].

Hypothermia may have neuroprotective effects through multiple mechanisms of action. Hypothermia reduces cerebral oxygen demand, excitotoxicity, and inflammation. Moderate hypothermia (32 to 34° C) improves neurologic outcomes in adult cardiac arrest patients and reduces mortality [52,53]. In neonates who have perinatal asphyxia, hypothermia reduces mortality and severe disability [54,55].

Early trials suggest that both intravascular and surface cooling methods are feasible [56,57]. Surface cooling methods include simple measures like

cooling blankets and ice packing, and adherent cooling jackets, pads, and head wraps [58]. Endovascular cooling can be accomplished by administering large amounts of chilled saline [59]. Newer cooling catheters, however, exchange heat by means of transduction, eliminating many of the problems associated with high-volume infusions [60] (Fig. 4).

Hypothermia, in a conscious stroke patient, carries additional risks and complications. After cardiac arrest, patients are treated with neuromuscular blockers and sedating medications to ameliorate the shivering response. In stroke patients, early detection of clinical deterioration may be critical; therefore, induced hypothermia without sedation and paralysis is desirable. The shivering response may be managed with a meperidine patient-controlled analgesia pump [61] in conjunction [44] with buspirone [62]. Induced hypothermia is labor-intensive and requires intensive care monitoring. Hypothermia is being tested both alone and in combination with thrombolysis and caffeinol [58].

Experimental evidence and clinical evidence suggest that the hydroxymethylglutaryl coenzyme A reductase inhibitors or statins have effects beyond

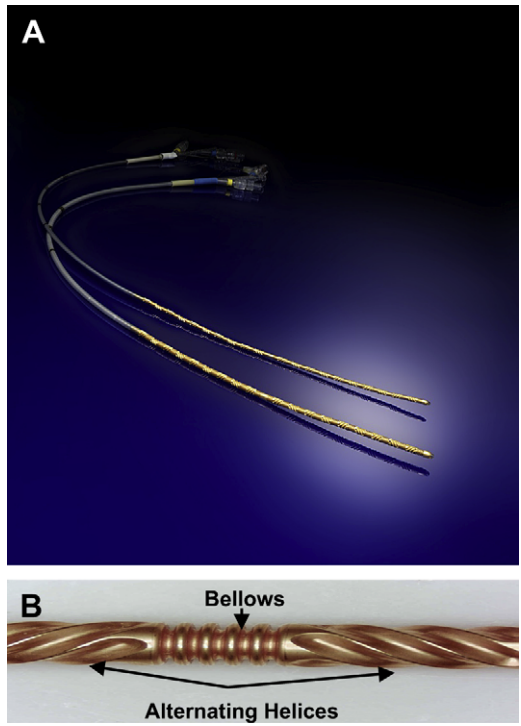

Fig. 4. Celsius Control Catheter. Intravascular cooling devices circulate fluid internally and cool via transduction. The Celsius Control catheter (*A*). Helices and bellows along the catheter (*B*) improve the cooling of circulating blood. (*Courtesy of* Innercool Therapies, Incorporated, San Diego, California; with permission.)

lowering cholesterol. Statins also have beneficial effects on endothelial function, coronary and cerebral blood flow, inflammation, and hemostasis [63,64]. Atorvastatin initiated within 24 hours after ischemic stroke has been reported to improve functional and neurologic recovery, despite no effect on infarct volume [65]. Further research will determine if statins can reduce infarct burden and disability after ischemic stroke.

The future of neuroprotection is promising. Trial design, however, is critical for success, and principles have been outlined to guide future trials [66]. Furthermore, combinations of multiple neuroprotection strategies may be more effective than individual therapies alone [49,67–69].

General medical management

As with any acute disease process, airway maintenance and adequate oxygenation are crucial to therapeutic success. Stroke patients who have reduced consciousness or brainstem involvement are at increased risk of airway compromise [70]. Endotracheal intubation may be required for these patients if they are unable to protect the airway or maintain adequate gas exchange [71]. The recommended target oxygen saturation in an acute stroke patient is greater than or equal to 95% [2]. The use of supplemental oxygen is of unproven benefit [72,73], and should be used only if required to maintain adequate oxygen saturation.

Hypothermia has been discussed as a potential strategy for neuroprotection. Hyperthermia has been associated with unfavorable neurologic outcome and increased mortality [74,75]. Even a simple 1° C reduction in body temperature almost doubles the chance of a favorable outcome [76]. Patients with fever should be evaluated thoroughly for the underlying etiology, and fever should be controlled. Measures to control fever include antipyretic medications, such as acetaminophen or ibuprofen, and cooling devices.

Hypoglycemia commonly presents with symptoms suggestive of AIS [2], and correcting the hypoglycemia should lead to a rapid resolution of the neurologic deficits. Hyperglycemia is present in up to one third of patients who have AIS [77] and is associated with worse outcomes than those with euglycemia [78], even in patients treated with thrombolytics [79]. Hyperglycemia has widespread negative effects during anaerobic glycolysis including regional lactic acidosis and free radical production. In addition, increased serum glucose may be associated with development of brain edema after stroke [80], and an increased risk of hemorrhagic transformation [81].

Despite being a well-known predictor of poor outcome, the effect of hyperglycemia treatment on outcomes is unclear. Intensive insulin protocols have been shown to be beneficial in critically ill patients, with goal blood glucose 70 to 110 mg/dL [82]. Additional clinical trial results are needed to determine the effectiveness of insulin protocols after AIS for improving outcomes [83]. In lieu of further data, the recommended approach is to treat hyperglycemia if the blood glucose level is greater than 200 mg/dL [2].

Hypotension is rare in AIS patients. When present, however, it is another predictor of an unfavorable outcome [84]. Potential causes for hypotension in patients who have AIS include aortic dissection, dehydration, blood loss, sepsis, and decreased cardiac output [2]. If hypotension is noted, immediate treatment should be initiated and an underlying cause sought.

Hypertension at presentation is found in most patients who have AIS [85]. Possible etiologies include acute stress, pain, hypoxia, or increased intracranial pressure. A U-shaped relationship between admission BP and mortality has been observed (Fig. 5) [86,87].

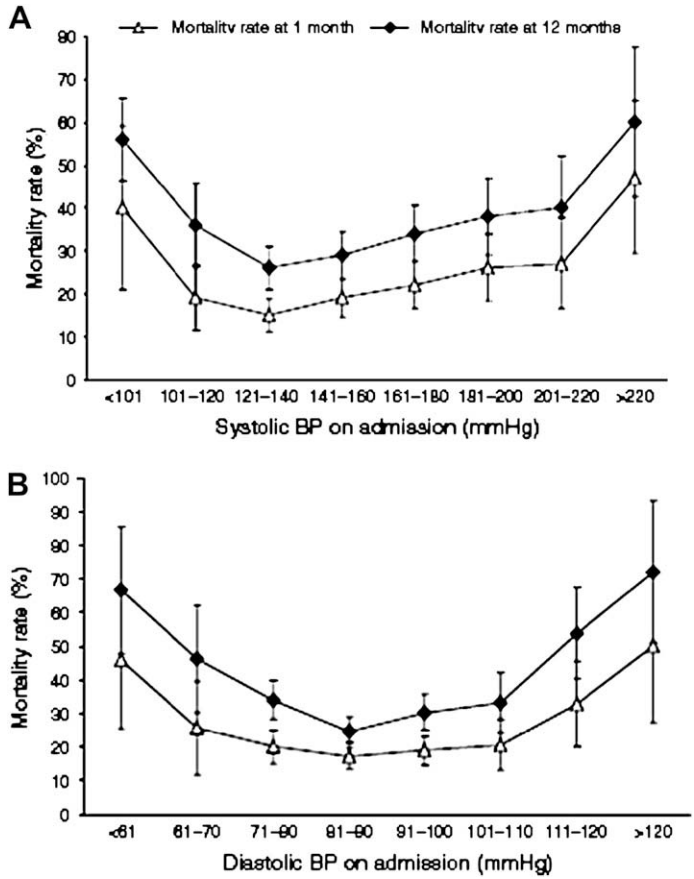

Fig. 5. Blood pressure on presentation and mortality. Line graphs showing the relationship between blood pressure on presentation and stroke mortality at 1 and 12 months. (*A*) Systolic blood pressure and (*B*) Diastolic blood pressure. Triangles and squares indicate early and late stroke mortality, respectively. 95% confidence intervals are indicated by T-bars. (*From* Vemmos KN, Tsivgoulis G, Spengos K, et al. U-shaped relationship between mortality and admission blood pressure in patients with acute stroke. J Intern Med 2004;255(2):260; with permission).

Possible advantages of inducing hypertension include improving collateral perfusion and blood flow through high-grade vascular stenoses. Animal models and small clinical studies suggest that drug-induced hypertension with phenylephrine may be beneficial in AIS [88–90]. Potential adverse effects of vasopressor infusions, however, are serious and include myocardial infarction, pulmonary edema, and systemic end organ ischemia. Furthermore, the safety and benefit of induced hypertension in people remain unproven, and it is not recommended in AIS outside of clinical trials [2].

Despite the observational data, optimal BP management after AIS remains unclear. Acutely lowering BP may decrease the risk of hemorrhagic transformation and cerebral edema. Actively lowering BP, however may lead to neurologic worsening by increasing ischemia in the penumbra [91].

The data so far are inconclusive. Spontaneous or iatrogenic reductions in BP greater than 20 mmHg have been associated with neurologic worsening, larger infarctions, and increased mortality [85]. Also, early administration (within 24 hours of admission) of antihypertensive agents in patients who have AIS with systolic blood pressure (SBP) greater than 180 mm Hg has been associated with neurologic deterioration, poor outcome, and mortality [85]. Conversely, reductions in BP in the first week after AIS also have been associated with improved short-term outcomes [92]. Large, well-designed trials are needed to clarify the most appropriate management of BP after AIS. BP greater than 185/110 mm Hg after thrombolysis has been associated with an increased risk of hemorrhagic transformation [7,22].

Recommendations for BP lowering after AIS are summarized in Table 1. The consensus is that antihypertensive medication should be withheld unless the SBP is greater than 220 mm Hg or the DBP is greater than 120 mm Hg

Table 1
Blood pressure management acute ischemic stroke

Blood pressure (mm Hg)	Treatment
In patients not eligible for thrombolysis or other acute reperfusion therapies	
SBP $\leq$220 or DBP $\leq$120	Observation
SBP $>$220 or DBP 121–140	Enalaprilat (intravenous [IV]) or Hydralazine (IV) or Labetalol (IV) or Clonidine (IV or subcutaneous) or Nicardipine infusion (IV)
DBP $>$140	Nicardipine infusion (IV) or Nitroprusside infusion (IV)
B. In patients eligible for thrombolysis or other acute reperfusion therapies	
SBP $\leq$185 or DBP $\leq$110	Observation
SBP $>$185 or DBP $>$110	Labetalol (IV) or Hydralazine (IV) or Clonidine (IV or Subcutaneous) or Nicardipine Infusion (IV)
DBP $>$140	Nicardipine infusion (IV) or Nitroprusside infusion (IV)

in patients who have AIS but are not eligible for IV rt-PA. Patients eligible for thrombolysis should have a goal SBP of less than 185 mm Hg and DBP of less than 110 mm Hg [2]. Angiotensin converting enzyme inhibitors are not recommended for BP lowering in patients eligible for thrombolysis. This is because of concern over orolingual angioedema, a rare but potentially serious allergic reaction that is reported to occur more commonly when this class of medications is used with IV rt-PA [93].

Summary

Thrombolysis with IV rt-PA within 3 hours of symptom onset remains the only FDA- approved medical therapy for AIS. The MERCI concentric retriever and Penumbra device, however, also have been approved for mechanical embolectomy in cerebral arteries, but the effect on outcomes remains uncertain. Multiple other acute reperfusion strategies are being tested that hopefully have improve reperfusion efficiency and extend the treatment window.

Despite earlier disappointments, there is renewed enthusiasm for neuroprotection therapies. Improved trial designs and combining various neuroprotective strategies may help achieve success.

With the increasing emphasis on thrombolysis and neuroprotection, the importance of good general medical management cannot be forgotten. Defining optimal management of serum glucose, temperature, and BP is vital to achieving favorable outcomes in ischemic stroke.

References

[1] Jones TH, Morawetz RB, Crowell RM, et al. Thresholds of focal cerebral ischemia in awake monkeys. J Neurosurg 1981;54(6):773–82.

[2] Adams HP Jr, del Zoppo G, Alberts MJ, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups. The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. Stroke 2007; 38(5):1655–711.

[3] Bruno A, Biller J, Adams HP Jr, et al. Acute blood glucose level and outcome from ischemic stroke. Trial of ORG 10172 in Acute Stroke Treatment (TOAST) investigators. Neurology 1999;52(2):280–4.

[4] Reith J, Jorgensen HS, Pedersen PM, et al. Body temperature in acute stroke: relation to stroke severity, infarct size, mortality, and outcome. Lancet 1996;347(8999):422–5.

[5] Baron JC. Mapping the ischaemic penumbra with PET: implications for acute stroke treatment. Cerebrovasc Dis 1999;9(4):193–201.

[6] The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995;333(24):1581–7.

[7] The NINDS t-PA Stroke Study Group. Intracerebral hemorrhage after intravenous t-PA therapy for ischemic stroke. Stroke 1997;28(11):2109–18.

[8] Khatri P, Wechsler LR, Broderick JP. Intracranial hemorrhage associated with revascularization therapies. Stroke 2007;38(2):431–40.
[9] Broderick J, Connolly S, Feldmann E, et al. Guidelines for the management of spontaneous intracerebral hemorrhage in adults: 2007 update. A guideline from the American Heart Association/American Stroke Association Stroke Council, High Blood Pressure Research Council, and the Quality of Care and Outcomes in Research Interdisciplinary Working Group. Stroke 2007;38(6):2001–23.
[10] Katzan IL, Furlan AJ, Lloyd LE, et al. Use of tissue-type plasminogen activator for acute ischemic stroke: the Cleveland area experience. JAMA 2000;283(9):1151–8.
[11] Katzan IL, Hammer MD, Hixson ED, et al. Utilization of intravenous tissue plasminogen activator for acute ischemic stroke. Arch Neurol 2004;61(3):346–50.
[12] Graham GD. Tissue plasminogen activator for acute ischemic stroke in clinical practice: a meta-analysis of safety data. Stroke 2003;34(12):2847–50.
[13] Khaja AM, Grotta JC. Established treatments for acute ischaemic stroke. Lancet 2007; 369(9558):319–30.
[14] Tanne D, Kasner SE, Demchuk AM, et al. Markers of increased risk of intracerebral hemorrhage after intravenous recombinant tissue plasminogen activator therapy for acute ischemic stroke in clinical practice: the Multicenter rt-PA Stroke Survey. Circulation 2002; 105(14):1679–85.
[15] van Oostenbrugge RJ, Hupperts RM, Lodder J. Thrombolysis for acute stroke with special emphasis on the very old: experience from a single Dutch centre. J Neurol Neurosurg Psychiatry 2006;77(3):375–7.
[16] Engelter ST, Reichhart M, Sekoranja L, et al. Thrombolysis in stroke patients aged 80 years and older: Swiss survey of IV thrombolysis. Neurology 2005;65(11):1795–8.
[17] Sylaja PN, Cote R, Buchan AM, et al. Thrombolysis in patients older than 80 years with acute ischaemic stroke: Canadian Alteplase for Stroke Effectiveness Study. J Neurol Neurosurg Psychiatry 2006;77(7):826–9.
[18] Barber PA, Zhang J, Demchuk AM, et al. Why are stroke patients excluded from TPA therapy? An analysis of patient eligibility. Neurology 2001;56(8):1015–20.
[19] Smith EE, Abdullah AR, Petkovska I, et al. Poor outcomes in patients who do not receive intravenous tissue plasminogen activator because of mild or improving ischemic stroke. Stroke 2005;36(11):2497–9.
[20] Gonzales N, Albright K, Noser E, et al. Mild stroke should not exclude patients from thrombolytic therapy. Stroke 2006;37(2):621.
[21] Patel SC, Levine SR, Tilley BC, et al. Lack of clinical significance of early ischemic changes on computed tomography in acute stroke. JAMA 2001;286(22):2830–8.
[22] Larrue V, von Kummer R, del Zoppo G, et al. Hemorrhagic transformation in acute ischemic stroke. Potential contributing factors in the European Cooperative Acute Stroke Study. Stroke 1997;28(5):957–60.
[23] Larrue V, von Kummer RR, Muller A, et al. Risk factors for severe hemorrhagic transformation in ischemic stroke patients treated with recombinant tissue plasminogen activator: a secondary analysis of the European–Australasian Acute Stroke Study (ECASS II). Stroke 2001;32(2):438–41.
[24] Demchuk AM, Hill MD, Barber PA, et al. Importance of early ischemic computed tomography changes using ASPECTS in NINDS rtPA Stroke Study. Stroke 2005;36(10):2110–5.
[25] Smith WS. Safety of mechanical thrombectomy and intravenous tissue plasminogen activator in acute ischemic stroke. Results of the Multimechanical Embolus Removal in Cerebral Ischemia (MERCI) trial, part I. AJNR Am J Neuroradiol 2006;27(6):1177–82.
[26] The Penumbra Stroke Trial Investigators. The penumbra stroke trial: safety and effectiveness of a new generation of mechanical devices for clot removal in acute ischemic stroke. Stroke 2008;39(2):527–729.

[27] Lewandowski CA, Frankel M, Tomsick TA, et al. Combined intravenous and intra-arterial r-TPA versus intra-arterial therapy of acute ischemic stroke: emergency management of stroke (EMS) bridging trial. Stroke 1999;30(12):2598–605.
[28] The IMS Study Investigators. Combined intravenous and intra-arterial recanalization for acute ischemic stroke: the Interventional Management of Stroke Study. Stroke 2004;35(4): 904–11.
[29] Shaltoni HM, Albright KC, Gonzales NR, et al. Is intra-arterial thrombolysis safe after full-dose intravenous recombinant tissue plasminogen activator for acute ischemic stroke? Stroke 2007;38(1):80–4.
[30] Nedeltchev K, Brekenfeld C, Remonda L, et al. Internal carotid artery stent implantation in 25 patients with acute stroke: preliminary results. Radiology 2005;237(3):1029–37.
[31] Bukow SC, Daffertshofer M, Hennerici MG. Tirofiban for the treatment of ischaemic stroke. Expert Opin Pharmacother 2006;7(1):73–9.
[32] Sugg RM, Pary JK, Uchino K, et al. Argatroban TPA Stroke Study: study design and results in the first-treated cohort. Arch Neurol 2006;63(8):1057–62.
[33] The Multicenter Acute Stroke Trial—Europe Study Group. Thrombolytic therapy with streptokinase in acute ischemic stroke. N Engl J Med 1996;335(3):145–50.
[34] Haley EC Jr, Lyden PD, Johnston KC, et al. A pilot dose-escalation safety study of tenecteplase in acute ischemic stroke. Stroke 2005;36(3):607–12.
[35] Sacco RL, Chong JY, Prabhakaran S, et al. Experimental treatments for acute ischaemic stroke. Lancet 2007;369(9558):331–41.
[36] Liu M, Counsell C, Zhao XL, et al. Fibrinogen-depleting agents for acute ischaemic stroke. Cochrane Database Syst Rev 2003;3:CD000091.
[37] Hennerici MG, Kay R, Bogousslavsky J, et al. Intravenous ancrod for acute ischaemic stroke in the European stroke treatment with ancrod trial: a randomised–controlled trial. Lancet 2006;368(9550):1871–8.
[38] Hacke W, Albers G, Al-Rawi Y, et al. The desmoteplase in acute ischemic stroke trial (DIAS): a phase II MRI-based 9-hour window acute stroke thrombolysis trial with intravenous desmoteplase. Stroke 2005;36(1):66–73.
[39] Lauer CG, Burge R, Tang DB, et al. Effect of ultrasound on tissue-type plasminogen activator-induced thrombolysis. Circulation 1992;86(4):1257–64.
[40] Alexandrov AV, Molina CA, Grotta JC, et al. Ultrasound-enhanced systemic thrombolysis for acute ischemic stroke. N Engl J Med 2004;351(21):2170–8.
[41] Daffertshofer M, Gass A, Ringleb P, et al. Transcranial low-frequency ultrasound-mediated thrombolysis in brain ischemia: increased risk of hemorrhage with combined ultrasound and tissue plasminogen activator: results of a phase II clinical trial. Stroke 2005; 36(7):1441–6.
[42] Hacke W, Donnan G, Fieschi C, et al. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. Lancet 2004; 363(9411):768–74.
[43] Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with Alteplase 3 to 4.5 hours after acute ischemic stroke. N Eng J Med 2008;359(13):1317–29.
[44] Albers GW, Thijs VN, Wechsler L, et al. Magnetic resonance imaging profiles predict clinical response to early reperfusion: the diffusion and perfusion imaging evaluation for understanding stroke evolution (DEFUSE) study. Ann Neurol 2006;60(5):508–17.
[45] CAST (Chinese Acute Stroke Trial) Collaborative Group. CAST: randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. Lancet 1997; 349(9066):1641–9.
[46] International Stroke Trial Collaborative Group. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. Lancet 1997;349(9065):1569–81.

[47] Harrington RA, Becker RC, Ezekowitz M, et al. Antithrombotic therapy for coronary artery disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126(3 Suppl):513S–48S.
[48] Meyer DM, Albright KC, Allison TA, et al. LOAD: a pilot study of the safety of loading of aspirin and clopidogrel in acute ischemic stroke and transient ischemic attack. J Stroke Cerebrovasc Dis 2008;17(1):26–9.
[49] Stroke Therapy Academic Industry Roundtable II. Recommendations for clinical trial evaluation of acute stroke therapies. Stroke 2001;32(7):1598–606.
[50] Saver JL, Kidwell C, Eckstein M, et al. Prehospital neuroprotective therapy for acute stroke: results of the Field Administration of Stroke Therapy—Magnesium (FAST-MAG) pilot trial. Stroke 2004;35(5):e106–8.
[51] Aronowski J, Strong R, Shirzadi A, et al. Ethanol plus caffeine (caffeinol) for treatment of ischemic stroke: preclinical experience. Stroke 2003;34(5):1246–51.
[52] The Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002;346(8):549–56.
[53] Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 2002;346(8):557–63.
[54] Gluckman PD, Wyatt JS, Azzopardi D, et al. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. Lancet 2005; 365(9460):663–70.
[55] Shankaran S, Laptook AR, Ehrenkranz RA, et al. Whole-body hypothermia for neonates with hypoxic–ischemic encephalopathy. N Engl J Med 2005;353(15):1574–84.
[56] Krieger DW, De Georgia MA, Abou-Chebl A, et al. Cooling for acute ischemic brain damage (COOL AID): an open pilot study of induced hypothermia in acute ischemic stroke. Stroke 2001;32(8):1847–54.
[57] De Georgia MA, Krieger DW, Abou-Chebl A, et al. Cooling for Acute Ischemic Brain Damage (COOL AID): a feasibility trial of endovascular cooling. Neurology 2004;63(2):312–7.
[58] Hemmen TM, Lyden PD. Induced hypothermia for acute stroke. Stroke 2007;38(2 Suppl): 794–9.
[59] Baumgardner JE, Baranov D, Smith DS, et al. The effectiveness of rapidly infused intravenous fluids for inducing moderate hypothermia in neurosurgical patients. Anesth Analg 1999;89(1):163–9.
[60] Mack WJ, Huang J, Winfree C, et al. Ultrarapid, convection-enhanced intravascular hypothermia: a feasibility study in nonhuman primate stroke. Stroke 2003;34(8):1994–9.
[61] Alfonsi P, Sessler DI, Du Manoir B, et al. The effects of meperidine and sufentanil on the shivering threshold in postoperative patients. Anesthesiology 1998;89(1):43–8.
[62] Mokhtarani M, Mahgoub AN, Morioka N, et al. Buspirone and meperidine synergistically reduce the shivering threshold. Anesth Analg 2001;93(5):1233–9.
[63] Amarenco P, Labreuche J, Lavallee P, et al. Statins in stroke prevention and carotid atherosclerosis: systematic review and up-to-date meta-analysis. Stroke 2004;35(12):2902–9.
[64] Ballantyne CM. Current and future aims of lipid-lowering therapy: changing paradigms and lessons from the Heart Protection Study on standards of efficacy and safety. Am J Cardiol 2003;92(4B):3K–9K.
[65] Chen J, Zhang ZG, Li Y, et al. Statins induce angiogenesis, neurogenesis, and synaptogenesis after stroke. Ann Neurol 2003;53(6):743–51.
[66] Hickenbottom SL, Grotta J. Neuroprotective therapy. Semin Neurol 1998;18(4):485–92.
[67] Stroke Therapy Academic Industry Roundtable. Recommendations for standards regarding preclinical neuroprotective and restorative drug development. Stroke 1999;30(12):2752–8.
[68] Fisher M. Recommendations for advancing development of acute stroke therapies: stroke therapy academic industry roundtable 3. Stroke 2003;34(6):1539–46.
[69] Fisher M, Albers GW, Donnan GA, et al. Enhancing the development and approval of acute stroke therapies: stroke therapy academic industry roundtable. Stroke 2005;36(8):1808–13.

[70] Grotta J, Pasteur W, Khwaja G, et al. Elective intubation for neurologic deterioration after stroke. Neurology 1995;45(4):640–4.
[71] Hacke W, Krieger D, Hirschberg M. General principles in the treatment of acute ishemic stroke. Cerebrovasc Dis 1991;1(Suppl 1):93–9.
[72] Ronning OM, Guldvog B. Should stroke victims routinely receive supplemental oxygen? A quasi-randomized controlled trial. Stroke 1999;30(10):2033–7.
[73] Treib J, Grauer MT, Woessner R, et al. Treatment of stroke on an intensive stroke unit: a novel concept. Intensive Care Med 2000;26(11):1598–611.
[74] Azzimondi G, Bassein L, Nonino F, et al. Fever in acute stroke worsens prognosis. A prospective study. Stroke 1995;26(11):2040–3.
[75] Ginsberg MD, Busto R. Combating hyperthermia in acute stroke: a significant clinical concern. Stroke 1998;29(2):529–34.
[76] Jorgensen HS, Reith J, Nakayama H, et al. What determines good recovery in patients with the most severe strokes? The Copenhagen Stroke Study. Stroke 1999;30(10):2008–12.
[77] Scott JF, Robinson GM, French JM, et al. Prevalence of admission hyperglycaemia across clinical subtypes of acute stroke. Lancet 1999;353(9150):376–7.
[78] Bruno A, Levine SR, Frankel MR, et al. Admission glucose level and clinical outcomes in the NINDS r-TPA stroke trial. Neurology 2002;59(5):669–74.
[79] Alvarez-Sabin J, Molina CA, Ribo M, et al. Impact of admission hyperglycemia on stroke outcome after thrombolysis: risk stratification in relation to time to reperfusion. Stroke 2004;35(11):2493–8.
[80] Lindsberg PJ, Roine RO. Hyperglycemia in acute stroke. Stroke 2004;35(2):363–4.
[81] Kase CS, Furlan AJ, Wechsler LR, et al. Cerebral hemorrhage after intra-arterial thrombolysis for ischemic stroke: the PROACT II trial. Neurology 2001;57(9):1603–10.
[82] Van den Berghe G, Wouters PJ, Bouillon R, et al. Outcome benefit of intensive insulin therapy in the critically ill: insulin dose versus glycemic control. Crit Care Med 2003;31(2): 359–66.
[83] Gray CS, Hildreth AJ, Alberti GK, et al. Poststroke hyperglycemia: natural history and immediate management. Stroke 2004;35(1):122–6.
[84] Leonardi-Bee J, Bath PM, Phillips SJ, et al. Blood pressure and clinical outcomes in the International Stroke Trial. Stroke 2002;33(5):1315–20.
[85] Castillo J, Leira R, Garcia MM, et al. Blood pressure decrease during the acute phase of ischemic stroke is associated with brain injury and poor stroke outcome. Stroke 2004; 35(2):520–6.
[86] Vemmos KN, Spengos K, Tsivgoulis G, et al. Factors influencing acute blood pressure values in stroke subtypes. J Hum Hypertens 2004;18(4):253–9.
[87] Vemmos KN, Tsivgoulis G, Spengos K, et al. U-shaped relationship between mortality and admission blood pressure in patients with acute stroke. J Intern Med 2004;255(2):257–65.
[88] Rordorf G, Cramer SC, Efird JT, et al. Pharmacological elevation of blood pressure in acute stroke. Clinical effects and safety. Stroke 1997;28(11):2133–8.
[89] Rordorf G, Koroshetz WJ, Ezzeddine MA, et al. A pilot study of drug-induced hypertension for treatment of acute stroke. Neurology 2001;56(9):1210–3.
[90] Wityk RJ, Restrepo L. Hypoperfusion and its augmentation in patients with brain ischemia. Curr Treat Options Cardiovasc Med 2003;5(3):193–9.
[91] Johnston KC, Mayer SA. Blood pressure reduction in ischemic stroke: a two-edged sword? Neurology 2003;61(8):1030–1.
[92] Rodriguez-Garcia JL, Botia E, de La Sierra A, et al. Significance of elevated blood pressure and its management on the short-term outcome of patients with acute ischemic stroke. Am J Hypertens 2005;18(3):379–84.
[93] Hill MD, Lye T, Moss H, et al. Hemi-orolingual angioedema and ACE inhibition after alteplase treatment of stroke. Neurology 2003;60(9):1525–7.