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

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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.
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 circulating 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 effect 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
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.

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**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.
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

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**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 to 180 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

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
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. At 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
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 0.9 mg/kg. 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

![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.)](image-url)
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, Tsvigoulis 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.

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<tr>
<th>Blood pressure (mm Hg)</th>
<th>Treatment</th>
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<tr>
<td>In patients not eligible for thrombolysis or other acute reperfusion therapies</td>
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<tr>
<td>SBP ≤ 220 or DBP ≤ 120</td>
<td>Observation</td>
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<tr>
<td>SBP &gt; 220 or DBP 121–140</td>
<td>Enalaprilat (intravenous [IV]) or Hydralazine (IV) or Labetalol (IV) or Clonidine (IV or subcutaneous) or Nicardipine infusion (IV)</td>
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<td>DBP &gt; 140</td>
<td>Nicardipine infusion (IV) or Nitroprusside infusion (IV)</td>
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<td>B. In patients eligible for thrombolysis or other acute reperfusion therapies</td>
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<tr>
<td>SBP ≤ 185 or DBP ≤ 110</td>
<td>Observation</td>
</tr>
<tr>
<td>SBP &gt; 185 or DBP &gt; 110</td>
<td>Labetalol (IV) or Hydralazine (IV) or Clonidine (IV or Subcutaneous) or Nicardipine Infusion (IV)</td>
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<tr>
<td>DBP &gt; 140</td>
<td>Nicardipine infusion (IV) or Nitroprusside infusion (IV)</td>
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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


