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# Management of Acute Ischemic Stroke.

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Concise Definitive Review

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# Management of Acute Ischemic Stroke

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**Objectives:** Concise "synthetic" review of the state of the art of management of acute ischemic stroke.

**Data Sources:** Available literature on PubMed.

**Study Selection:** We selected landmark studies, recent clinical trials, observational studies, and professional guidelines on the management of stroke including the last 10 years.

**Data Extraction:** Eligible studies were identified and results leading to guideline recommendations were summarized.

**Data Synthesis:** Stroke mortality has been declining over the past 6 decades, and as a result, stroke has fallen from the second to the fifth leading cause of death in the United States. This trend may follow recent advances in the management of stroke, which highlight the importance of early recognition and early revascularization. Recent studies have shown that early recognition, emergency interventional treatment of acute ischemic stroke, and treatment in dedicated stroke centers can significantly reduce stroke-related morbidity and mortality. However, stroke remains the second leading cause of death worldwide and the number one cause for acquired long-term disability, resulting in a global annual economic burden.

**Conclusions:** Appropriate treatment of ischemic stroke is essential in the reduction of mortality and morbidity. Management of stroke involves a multidisciplinary approach that starts and extends beyond hospital admission. (*Crit Care Med* 2020; 48:1654–1663)

**Key Words:** cerebral edema; penumbra; secondary neuronal injury

Treatment of acute ischemic stroke (AIS) consists of a multidisciplinary approach that more than ever requires the involvement of the critical care specialist. Before the 1990s, treatment options for AIS were limited and mainly focused on symptomatic management, secondary prevention, and rehabilitation. Since then, the entire field was revolutionized by two major introductions. The first groundbreaking innovation that dramatically transformed acute stroke care on the basis of a National Institutes of Neurological Disease and Stroke (NINDS) landmark study was the Federal Drug Administration's (FDA) approval of IV tissue plasminogen activator (IV-tPA) in 1995 (1). IV-tPA remained the mainstay of treatment for about 2 decades until 2015 when more sophisticated clinical trials showed robust outcomes for endovascular therapy (EVT) (2). In the ICU, additional strategies aimed at optimizing patient's physiology can interface between triage and/or revascularization and discharge to rehabilitation.

## EARLY DETECTION

Ischemic stroke can occur both in the community and in the hospital and must be recognized by bystanders and/or providers. Early recognition activates a stroke-specific chain of survival (**Table 1**) (3). Stroke is a clinical diagnosis and several features of the patient's clinical presentation can be used to identify stroke patients (**Table 2**). Emergency Medical Systems are key in detection, triaging, and transport of stroke patients to receiving facilities.

## PREHOSPITAL MANAGEMENT

Workflows and organized systems of care can efficiently reduce delays in time to treatments (**Fig. 1**). With the deployment of mobile stroke units (MSUs) equipped with CT scanners and telemedicine links, recognition of patients and administration of treatments may be more precise and efficient. Recent studies have shown that the implementation of MSUs has led to higher rates and reduced the time to IV-tPA administration and door-to-needle time compared with regular ambulance transports to emergency departments (EDs) (4–8). In theory, initiation of therapies for intracerebral hemorrhage (ICH) such as blood pressure control and reversal of anticoagulation may also be implemented at the prehospital setting. In addition to clinical examination with conventional scales such as the Neurological Institutes of Health Stroke Scale (NIHSS), several prehospital scales and prompt recognition of severe strokes with large vessel occlusions (LVOs) have successfully been validated (**Table 3**) (9).

## EMERGENCY DEPARTMENT, STROKE TEAMS, AND STROKE CODE

A stroke team can provide around the clock services for patients with stroke. Such team consists of physicians with

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expertise in emergency medicine, vascular neurology/neurosurgery, and radiologists; advance care providers, nurses, clinical pharmacists, therapists, and technicians; and laboratory personnel (10). In the ED, the efficiency and accuracy of recognition of stroke syndromes can be performed with telemedicine (11). In the Stroke Team Remote Evaluation Using a Digital Observation Camera (STRokE-DOC) study, two-way audiovisual consultation was superior to telephone-based consultation in accurately identifying stroke patients, yielding a higher rate of IV-tPA administration with similar proportion in ICH but without effect on overall functional outcome (11). In the new era of recanalization for AIS with LVO (12), telemedicine systems have assisted in improving the recognition of stroke patients in need of endovascular therapies yielding to better functional outcomes and quality of life (13–16).

## NEUROIMAGING

Conventional noncontrast CT can be implemented at the prehospital level in specialized MSUs. A noncontrast CT scan has enough sensitivity to exclude hemorrhagic stroke such as subarachnoid hemorrhage or ICH. The Alberta Stroke Program Early CT Score (ASPECTS) was designed to determine middle cerebral artery (MCA) infarct severity using a noncontrast head CT scan. One point gets subtracted from the maximum score of 10 for any sign of early ischemia in each of the 10 predefined zones (ranges 0–10) (17) (**Fig. 2**). A patient with a high Rapid Arterial Occlusion Evaluation/NIHSS and normal looking brain or ASPECTS greater than 6 (Fig. 2*A*) means that infarction may not have set in and that revascularization strategies may be implemented. Early signs of infarction on CT or lower ASPECTS are usually associated with poor prognosis and hemorrhagic conversion (Fig. 2*B*). Timing to CT and reporting of preliminary data should be under 20 minutes according to current guidelines. A CT-angiography (CT-A) can effectively detect LVO and provide useful information about the patient's vascular anatomy and stroke etiology (**Fig. 3**) (18). Based on its rapid acquisition, many institutions now incorporate CT-perfusion (CT-P) technology to assess cerebral blood flow (CBF) by quantitative analysis of thresholds in time-to-maximum (T-max) transit and cerebral blood volumes. Quantification of ischemic "core" (CBF < 30%) and estimation of "penumbra" or tissue at risk (T-max > 6 s) can provide immediate information for treatment decision-making. Clinical trials have shown that perfusion mismatch ratios of core/penumbra greater than 1.8 may indicate the eligibility for EVT (**Fig. 4**) (19, 20). CT-P thresholds predicting infarction depend on the time from stroke symptom onset to imaging, time from imaging to reperfusion, and the quality of reperfusion (21). To this end, a process that includes advanced imaging with CT-A/CT-P or MRI should not delay IV thrombolysis or EVT.

## REVASCULARIZATION

The primary goal of advanced stroke management is revascularization and limitation of secondary neuronal injury. IV thrombolysis and EVT are now available for selected patients.

**TABLE 1. The 8 D's of Stroke Care**

| |
|---|
| Detection: Involves recognizing the signs and symptoms of an acute stroke (BEFAST, Table 2) |
| Dispatch: Activation of emergency medical services. In most cases, this involves calling 911 or a stroke team |
| Delivery: Means prompt transport of the patient to a hospital, preferably a stroke center or to a setting in the hospital for further evaluation by a stroke team |
| Door: This refers to the arrival of the patient at the ED. According to recommendations from the National Institute of Neurological Disorders and Stroke, an assessment should be completed by an ED physician within 10 min of arriving in the ED |
| Data: Data collection includes results from laboratory tests and both a physical and a neurologic examination (Neurological Institutes of Health Stroke Scale) |
| Decision: Information, such as the type of stroke, last seen normal, and time from onset of symptoms, is considered before a treatment decision is made |
| Drug/device: Fibrinolytic therapy should be administered within 4.5 hr of the onset of symptoms. Even if the patient is not a candidate for fibrinolysis, they may still qualify for endovascular therapy to remove mechanically a clot |
| Disposition: It is recommended that patients are admitted to an ICU or stroke unit within 3 hr of arrival in the ED |

ED = emergency department.
See Table 2 for BEFAST expansion.

### IV Thrombolysis

The first landmark clinical trial that demonstrated the safety and efficacy of IV-tPA in 1995 transitioned the treatment for AIS from being purely symptomatic to a highly time-sensitive matter. It shows that if IV-tPA is administered within the first 3 hours of symptom onset, patients are at least 30% more likely to have only minimal or no disability on the 90-day mark. Mortality difference between IV-tPA and placebo group was nonsignificant despite an increase in symptomatic hemorrhages in the treatment group (1). Although IV-tPA was the only AIS treatment until recently, the use of IV-tPA has been as low as 3.2–5.2% of all AIS patients in the United States (22). One major reason for the low treatment rate is the limited time window for IV-tPA. Based on the European study Thrombolysis with Alteplase 3 to 4.5 Hours after Acute

**TABLE 2. BEFAST, Detection of Stroke**

| |
|---|
| Balance, acute or sudden onset of loss of balance or coordination |
| Eyes, blurred or unclear vision, double vision, and gaze preference |
| Facial weakness or facial asymmetry |
| Arm and/or leg weakness |
| Speech difficulty/slurring of speech |
| Time is brain, time to activate stroke system and stroke clock |

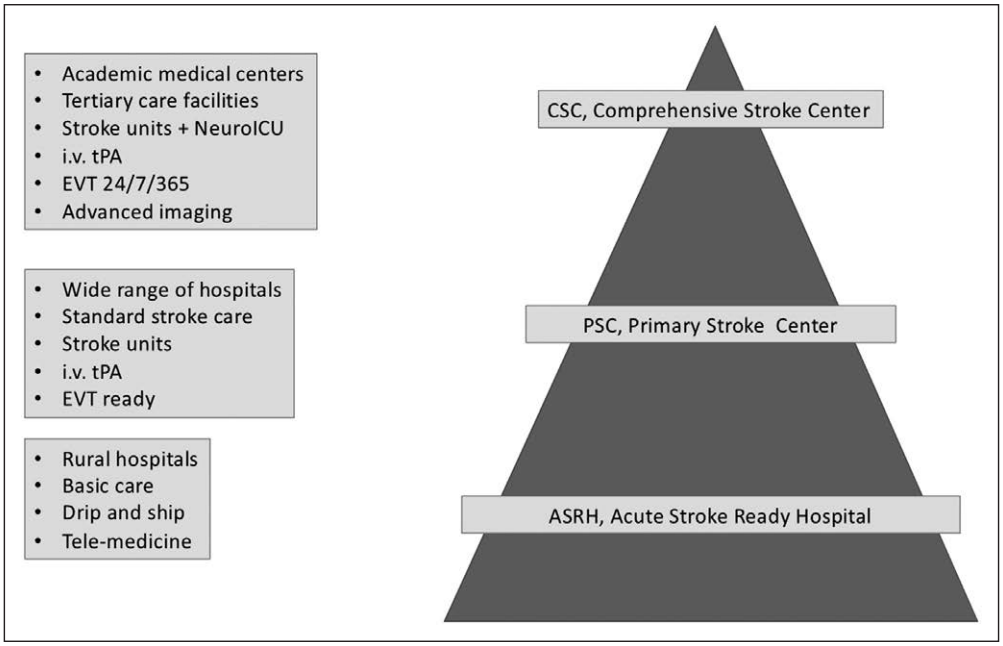


**Figure 1.** Organization of stroke centers. EVT = endovascular therapy, IV tPA = IV tissue plasminogen activator.

Ischemic Stroke (ECASS-3), the American Heart Association/American Stroke Association (AHA/ASA) extended the IV-tPA window from 3 to 4.5 hours in 2009 with additional exclusion criteria (22–24). This extension increased the utilization of IV-tPA by up to 20% (25).

Recently, clinical trials suggested that imaging rather than known time of onset (last seen normal) can guide clinicians to treat patients using the time discrepancies of acute stroke showing. Data from the European multicenter clinical trial MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset (WAKE-UP) suggest that almost 50% of wake-up strokes and daytime strokes of unknown onset are IV-tPA candidates when MRI criteria is used (26). However, cost, time spent in metal screening, and often far distance to the scanner are clear limitations to its implementation. In the Thrombolysis Guided by Perfusion Imaging up to 9 Hours after Onset of Stroke (EXTEND) clinical trial, CT-P imaging was used to assess the eligibility for IV-tPA and suggested that the efficacy and safety of IV-tPA can extend up to 9 hours and that revascularization can extend up to 24 hours (27).

Tenecteplase, a newer thrombolytic agent with high fibrinogen specificity and long half-life, allowing it to be given as a single bolus, had promising results in recent clinical trials. The Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke (EXTENT-IA-TNK) trial demonstrated that tenecteplase administration resulted in a higher reperfusion rate and a better functional outcome than alteplase in patients with AIS eligible for EVT (28, 29). Tenecteplase appears to be as efficacious, with a similar side-effect profile as alteplase when used in patients without LVO (30, 31). However, at this time, tenecteplase is not FDA-approved for IV thrombolysis in AIS patients and does not have the same level of recommendation by the AHA/ASA as alteplase. This could explain why many institutions have not adopted tenecteplase as a thrombolytic for AIS.

**TABLE 3. Rapid Arterial Occlusion Evaluation Scale**

| |
|---|
| Facial palsy: Absent (0), mild (1), and moderate (2) |
| Arm motor impairment: Normal to mild (0), moderate (1), and severe (2) |
| Leg motor impairment: Normal to mild (0), moderate (1), and severe (2) |
| Head/gaze deviation: Absent (0) and present (1) |
| Aphasia: Performs tasks correctly (0), performs one task correctly (1), and performs neither task (2) |
| Agnosia: Recognizes his/her arm and deficit (0), does recognize his/her arm but not or deficit (1), and does not recognize his/her arm or deficit (2) |

A score of ≥ 5, indicates higher likelihood of large vessel occlusion with 85% sensitivity and 68% specificity (9).

## Endovascular Therapy

The FDA approval of IV-tPA has innovated the entire field of emergency neurology. However, up to 69% of stroke patients are ineligible to receive IV-tPA due to delayed hospital presentation (32, 33). Over the last 3 years, the time window for AIS treatment has expanded thanks to EVT and has provided physicians with a stronger therapeutic arsenal. The success of EVT is measured by the degree or quality of revascularization. The Thrombolysis in Cerebral Infarction (TICI) scale is a tool to standardize the different degrees of reperfusion ranging from no perfusion (TICI 0) to complete perfusion (TICI 3) (**Table 4**) (34). TICI scores of 2B to 3 are usually regarded as successful reperfusion. Previous studies failed to show improved results with EVT and diminished the initial optimism regarding intervention for AIS (35–37). However, the study design of those clinical trials was criticized for not requiring the image proof of LVO, using older technology for clot retrieval, and having prolonged stroke to puncture times. Since 2015, multiple trials have shown the efficacy of EVT in addition to standard medical care in improving the overall outcome of AIS patients with proximal MCA or internal carotid artery (ICA) occlusion when EVT was performed within either 6 hours (20, 38–41), 8 hours (42), or 12 hours (43) of symptom onset. A pooled meta-analysis demonstrated that modern EVT more than doubles the odds of a better functional

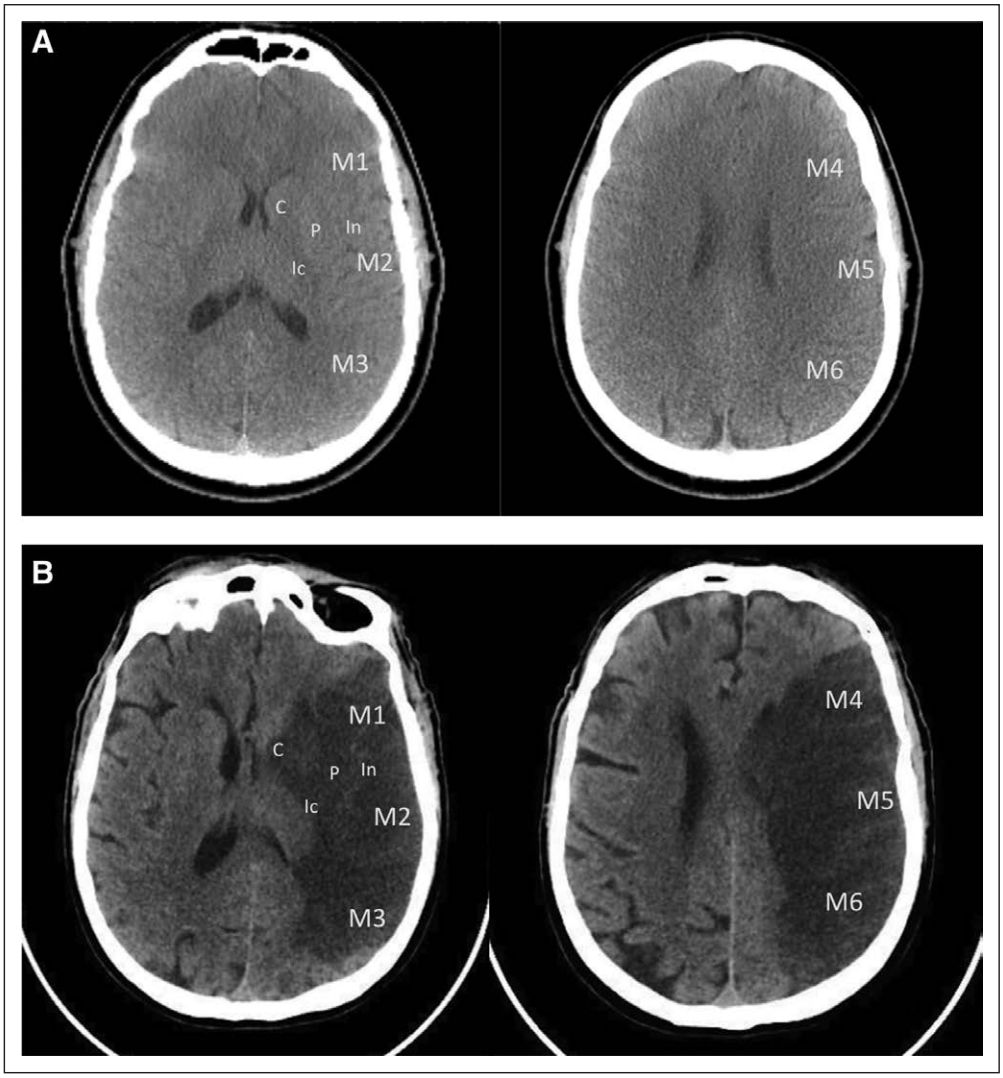


**Figure 2.** Alberta Stroke Program Early CT Score (ASPECTS). Scoring for each of the 10 zones. Each zone is graded either 1 (normal) or 0 (abnormal). The sum of all zones gives the ASPECTS. **A**, Normal looking brain with ASPECTS = 10. **B**, Brain with ischemic changes and ASPECTS less than 6. C = caudate, Ic = internal capsule, In = insular cortex, M = middle cerebral artery, P = putamen.

outcome compared with standard therapy alone without any significant difference in the mortality or risk of parenchymal hemorrhage at 90 days (2). Of 100 patients treated with EVT, 38 had a better functional outcome than the standard medical care. The number-needed-to-treat (NNT) for at least one patient to have a 1-point reduction on the modified Rankin Scale (mRS) is 2.6. The benefit of EVT remains substantial when only looked at the subset of patients that received IV-tPA prior to thrombectomy, and therefore, EVT should still be pursued after IV-tPA administration. It is also suggested that EVT should not be withheld only on the basis of age, and patients older than 80 years may also benefit from EVT (12). Two recent clinical trials showed that the time window can further be extended to 24 hours postsymptom onset if there is either mismatch between the clinical deficit and the infarct size or perfusion mismatch on imaging (19, 44). These trials are moving us away from an arbitrary clock time limit and transforming the way we think of stroke and the "biological clock." In most of these trials, the mean NIHSS was 16 or greater and further clinical trials are necessary to investigate the efficacy of EVT in LVO presenting as minor strokes (NIHSS < 5).

## ICU MANAGEMENT

### Oxygenation and Ventilation

Supplemental oxygen may be required if a patient's saturation is less than 94%. Rapid neurologic deterioration and ensuing loss of consciousness with impairment of reflexes that maintain the airway mandate definitive airway control. Failure to recognize imminent airway loss may result in complications such as aspiration, hypoxemia, and hypercapnia, which may result in secondary neuronal injury. Hyperbaric oxygen was shown to either have no effect or be harmful in AIS patients and should be avoided (45). For those critically ill AIS patients with respiratory failure and failure to wean off the ventilator, long-term tracheostomy may be required. The benefit of early tracheostomy is debatable but currently being studied under the Early Tracheostomy in Ventilated Stroke Patients 2 (SETPOINT-2) prospective clinical trial (ClinicalTrials.gov: NCT02377167).

### Blood Pressure

As part of cerebral autoregulation, blood pressure is commonly elevated during the acute phase of AIS, maximizing perfusion in the ischemic areas (46, 47). However, severe hypertension can lead to hemorrhagic transformation of the infarct, hypertensive encephalopathy, as well as cardiopulmonary and renal complications. Current AHA/ASA guidelines recommend permissive hypertension with a blood pressure goal of less than or equal to 220/120 mm Hg for the first 24–48 hours. Yet, these blood pressure variables only apply if the patient is not undergoing any acute intervention such as IV-tPA or EVT. If the patient receives IV-tPA, the risk of hemorrhagic transformation increases and the blood pressure should be lowered to less than or equal to 185/110 mm Hg prior to IV-tPA administration and to less than or equal to 180/105 mm Hg once IV-tPA has been given (48). Reperfusion injury and hemorrhagic transformation are of concern in the case of EVT; thus, blood pressure

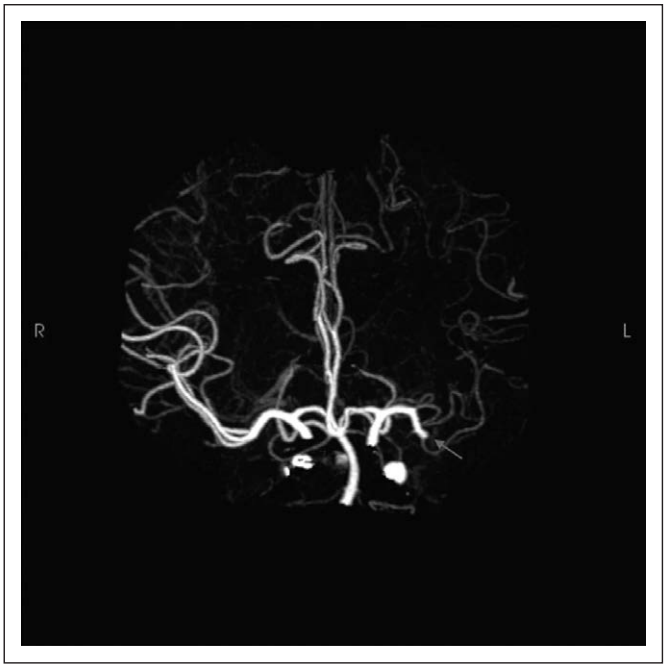


**Figure 3.** CT-angiography demonstrating an abrupt occlusion of the patient's left middle cerebral artery (*arrow*). L = left, R = right.

must be closely monitored during and after EVT. A retrospective cohort study suggests maintaining an MAP goal of 70–90 mm Hg during EVT to improve functional outcome (49). The current AHA/ASA guidelines recommend a post-EVT blood pressure of less than or equal to 180/105 mm Hg (48). However, that guideline does not consider the degree of reperfusion achieved during EVT. In patients with successful recanalization, defined as TICI 2b and TICI 3, the optimal postoperative blood pressure might be lower than that stated by the guidelines, to minimize the risk of reperfusion injury and ICH. A moderate blood pressure control with a systolic blood pressure goal less than or equal to 160 mm Hg was shown to reduce the incidence of ICH and mortality, if successful EVT was achieved (50). Anadani et al (51) demonstrated that a postprocedural blood pressure range from 121 to 140 mm Hg was associated with improved functional outcome compared with higher blood pressure, if the patients had successful recanalization. Given these data, it appears that blood pressure after EVT should be individualized based on the degree of recanalization.

Hypotension and hypovolemia should be avoided and corrected in patients with AIS. Etiologies for hypotension should ideally be sorted out with noninvasive modalities such as point-of-care ultrasound. While correcting hypovolemia, hypotonic solutions should be avoided due to the risk of increased edema formation. The usefulness of drug-induced hypertension is not well established, so the randomized multicenter Safety and Efficacy of Therapeutic INduced HYPERTENSION in Acute Non-cardioembolic Ischemic Stroke (SETIN-HYPERTENSION) clinical trial (ClinicalTrials.gov: NCT01600235) aims at determining the safety and efficacy of phenylephrine in patients with noncardioembolic stroke.

## Glycemic Control

Evidence indicates that persistent in-hospital hyperglycemia during the first 24 hours after AIS is associated with worse outcomes compared with normoglycemia due to multiple potential mechanisms, such as endothelial dysfunction, increased oxidative stress, and impaired fibrinolysis. However, in the NINDS funded Stroke Hyperglycemia Insulin Network Effort (SHINE) clinical trial, an intensive IV insulin protocol to achieve a systemic glucose between 80 and 130 mg/dL was not associated with favorable outcomes at 90 days compared with a standard regimen of insulin in a "sliding-scale" fashion to keep the glucose between 80 and 180 mg/dL (52). The intensive insulin protocol was associated with significant hypoglycemic events and a higher level of care. To this end, it is reasonable to treat hyperglycemia to achieve blood glucose levels in a range of 140–180 mg/dL and to monitor closely to prevent hypoglycemia in patients with AIS.

## Cerebral Edema

Large infarcts of the MCA or ICA are associated with high morbidity rates of up to 80%. Patients with large hemispheric infarcts (LHIs) are at increased risk of cerebral edema and fast neurologic deterioration that led to the term "malignant MCA infarction"(MMI) (53). Hypodensity seen in more than 50% of the MCA territory (Fig. 2*B*) or an infarct volume of greater than 145 cc within 14 hours of ictus are the most reliable predictors for a malignant course with increased intracranial pressure, herniation, and need for decompressive hemicraniectomy (DHC) (54). The ultimate intervention to alleviate increased intracranial pressure and avoid herniation in LHI with significant edema is surgical decompression with DHC. Three European clinical trials assessed the benefit of DHC in patients 60 years and younger (55–57). A pooled analysis of these trials showed that DHC does not only reduce mortality by 50% but also improve long-term functional outcome (58). The NNT to avoid a death is 2 (mRS = 6), whereas the NNT to avoid death and the most severe to moderately severe disability is 4 (mRS = 4–6). The proportion of patients alive with minimal-to-moderate disability (mRS = 0–3) was increased from 21% to 43%. Viewed another way, DHC resulted in a 49% absolute risk reduction in death, and an absolute increase in the proportion of patients rated as mRS = 2 of 12%, mRS = 3 of 10%, and mRS = 4 of 29% (58).

The DEcompressive Surgery for the Treatment of malignant INfarction of the middle cerebral arterY (DESTINY-II) clinical trial assessed the outcome of DHC in patients older than 60. It demonstrated that DHC increases the probability of survival, but most survivors had significant disabilities (mRS = 4–5) (59). In all these trials, DHC was performed within 48 hours, and currently, there is no indication for a "wait and see strategy" (e.g., waiting for neurologic deterioration or radiographic midline shift). However, the ideal timing of DHC is still unclear and more data including standardized medical management are necessary. Furthermore, it remains debatable what the definition of a favorable functional outcome is and what degree of disability is regarded as acceptable. Additional

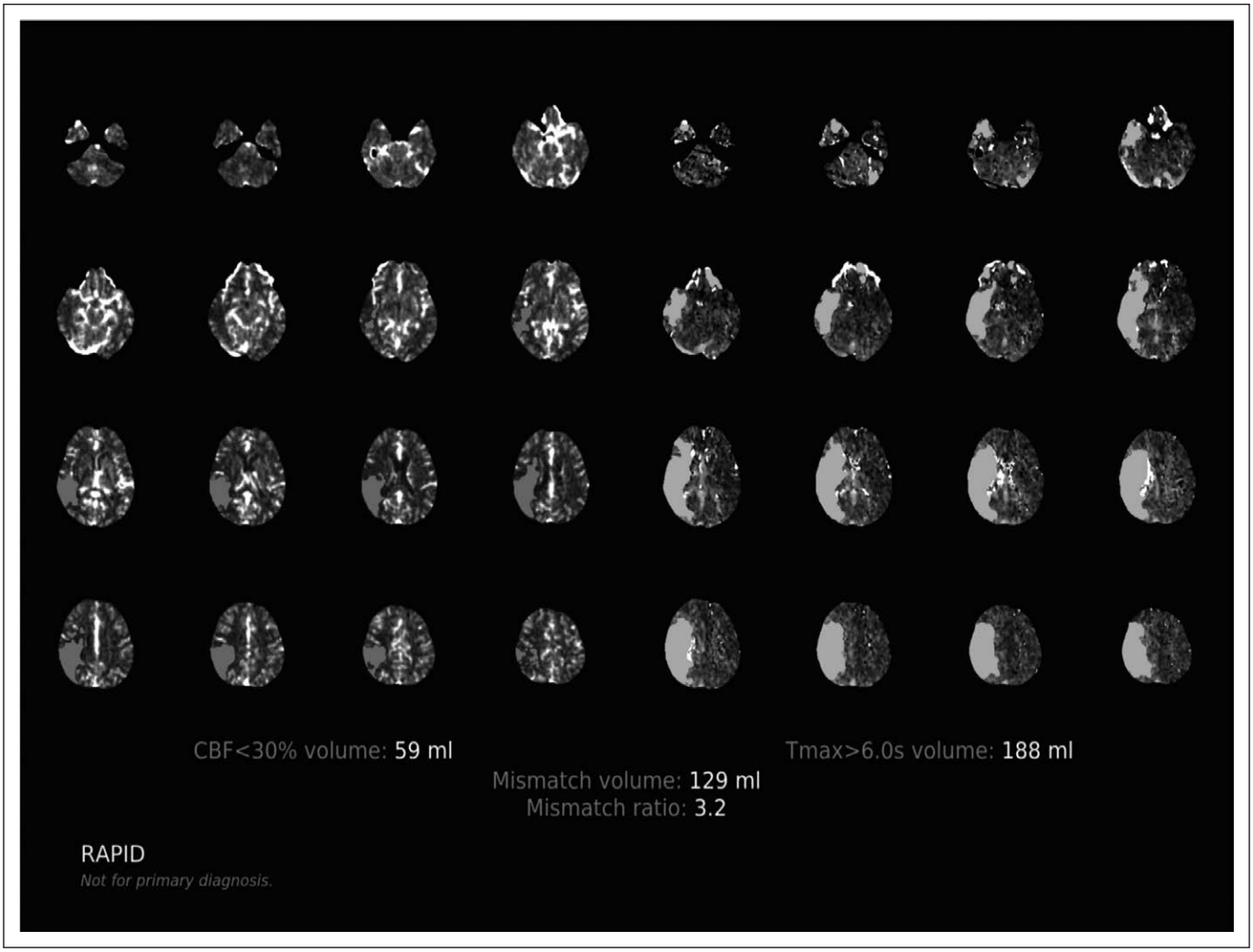


**Figure 4.** Mismatch ratio analysis of cerebral blood flow (CBF) by quantitative analysis of thresholds in time-to-maximum (T-max) to transit in a patient with a right middle cerebral artery occlusion. CBF in *dark gray* and T-max in *light gray*. A ratio of greater than 1.8 usually indicates eligibility for endovascular therapy. RAPID = rapid processing of perfusion and diffusion image analysis system.

surgical interventions that may be entertained in critically ill AIS patients are external ventricular drainage for the management of hydrocephalous and suboccipital craniectomy for posterior fossa/cerebellar infarcts with life-threatening cerebral edema.

In contrast to the three European DHC trials, the NINDS funded clinical trial Hemicraniectomy and durotomy upon deterioration from infarction-related swelling trial (HeADFIRST) did not find a mortality or morbidity benefit of DHC over a standardized medical treatment approach, which included normoglycemia (glucose < 200 mg/dL), permissive hypernatremia (sodium < 155 mEq/dL), and hyperosmolar therapy (60). This raises the question if a conservative approach should be trialed prior to DHC.

Data on the use of hyperosmolar therapy in MMI are scarce and the evidence for reducing ICP is mainly extrapolated from the traumatic brain injury literature. Despite the lack of clear evidence in MMI, hyperosmolar therapy with mannitol or hypertonic saline (HTS) has been proposed to reduce cytotoxic edema (61, 62). There is no definitive data whether one hyperosmolar agent is superior to the other, and the choice can be guided by their individual side effects. Potential complications of HTS use are fluid overload, pulmonary edema, hypokalemia, cardiac arrhythmias, hyperchloremic metabolic acidosis, acute kidney injury, and dilutional coagulopathy (63, 64). To avoid rebound edema, HTS should be gradually tapered and the serum sodium level should never be allowed to drop more than 10–12 mEq/L over 24 hours (63, 65). Potential complications of mannitol include acute kidney injury, hypotension due to diuresis, rebound ICP, electrolytic imbalance (hypo-/hypernatremia), and acid/base disturbances.

Glyburide, an IV sulfonylurea has been proposed as a potential agent for the management of cerebral edema due to its ionic properties at the sulfonylurea receptor-1-transient receptor potential melastatin-4 channel in neurons, astrocytes, and endothelium. The recent Safety and efficacy of intravenous glyburide on brain swelling after large hemispheric infarction (GAMES-RP) clinical trial demonstrated a substantial reduction in cerebral edema and midline shift without an impact on the outcomes (66). The industry-sponsored Phase 3 Study

**TABLE 4. Thrombolysis in Cerebral Infarction Scale**

| Grade | Radiographic Features |
|---|---|
| 0 | No perfusion beyond the point of occlusion |
| 1 | Penetration with minimal perfusion. Contrast passes the obstruction but fails to visualize the entire cerebral bed beyond the point of obstruction |
| 2 | Partial perfusion. Contrast passes the obstruction and visualized the cerebral bed past the obstruction. However, flow of contrast in the distal bed is slower than other, nonobstructed vessels |
| 2A | Only < 2/3 of entire vascular territory is visualized |
| 2B | Complete visualization of the vascular territory but with slower filling than normal |
| 3 | Complete perfusion. Entire vascular territory is visualized with normal flow |

Higashida et al (34).

to Evaluate the Efficacy and Safety of Intravenous BIIB093 (Glibenclamide) for Severe Cerebral Edema Following Large Hemispheric Infarction (CHARM) clinical trial testing a similar hypothesis with the sulfonylurea glibenclamide is underway (ClinicalTrials.gov: NCT0286495).

### Fever and Targeted Temperature Modulation

Observational studies have demonstrated the detrimental effects of fever on every outcome measure after stroke (67, 68). It appears that the effect of fever (temperature core [Tc] > 37.5°C) is pertinent to severely brain injured patients in the ICU (69). Clinical studies have shown the potential effect of therapeutic hypothermia (Tc, 34–35°C) for the management cerebral edema and intracranial hypertension. One study assessed the effect of targeted temperature modulation on mortality and neurologic outcome in patients with LHIs but failed to show a difference with a trend toward better functional outcome (70). Recently, the largest randomized clinical trial on therapeutic hypothermia after ischemic stroke European multicenter, randomized, phase III clinical trial of therapeutic hypothermia plus best medical treatment vs. best medical treatment alone for acute ischemic stroke (EURO-HYP) was stopped on the basis of futility. Similarly, the DEcompressive surgery Plus hypoTHermia for Space-Occupying Stroke (DEPTH-SOS) study, using therapeutic hypothermia and DHC after LHIs, was terminated early on the basis of harm in the therapeutic hypothermia arm (71). The ongoing Impact of Fever Prevention in Brain Injured Patients (INTREPID) randomized clinical trial is testing the hypothesis that early fever prevention to achieve normothermia (Tc = 37°C) after stroke is associated with improved outcomes (ClinicalTrials.gov: NCT02996266). Although there is paucity of high-quality data in support of fever control after ischemic stroke, it is recommended that patients with severe brain injury and fever refractory to medical therapy receive some degree of fever prevention while in the ICU (72).

### Rehabilitation

Early mobilization is thought to be of great importance in order to maximize functional recovery and independence after AIS. Animal models have shown that neuroplasticity and cortical reorganization, promoting functional improvement, peak 7–14 days after stroke and last for about 1 month (73). Early rehabilitation is thought to enhance further this dynamic post-stroke phase and help patients to gain compensatory mechanisms for remaining disabilities. Data show that even in ICU patients, early rehabilitation and intensity of rehabilitation sessions were associated with a better functional outcome (74). Yet, the optimal intensity and timing of early mobilization remain uncertain. The phase-III A Very Early Rehabilitation Trial after stroke (AVERT) clinical trial demonstrated that very early mobilization (< 24 hr after stroke) with frequent and prolonged rehabilitation sessions resulted in reduced favorable outcome. However, the dose-response analysis showed that short and frequent mobilizations may be beneficial early after acute stroke, whereas prolonged out-of-bed sessions reduce the odds of a good outcome (75). Furthermore, randomized controlled trials are needed to clarify those uncertainties.

### Nutrition

As in the case with all critically ill neurologic patients, enteral feeding should be started within 48 hours to avoid protein catabolism and malnutrition. A small-bore nasoduodenal feeding tube may reduce the risk of aspiration events. Assessment of speech and swallowing function is imperative in AIS patients to determine the need for long-term enteral nutrition with percutaneous enteric gastrostomy.

### Risk Factor Modification (Secondary Prevention)

Classification of AIS subtype/etiology is based on the definitions used in the multicenter Trial of Org 10172 in Acute Stroke Treatment and include the following: 1) large-artery atherosclerosis, 2) cardioembolism, 3) small-vessel occlusion, 4) stroke of other determined etiology, and 5) stroke of undetermined etiology (cryptogenic) (76). A thorough workup consisting of vascular imaging, MRI, transthoracic echocardiogram with bubble assessment (for shunt evaluation), lipid panel, and hemoglobin A1C, among others, is required to determine the underlying etiology and tailor the appropriate secondary stroke prevention. Antiplatelet therapy is an important cornerstone of treatment for the prevention of stroke and transient ischemic attacks (TIAs). Aspirin is the most commonly used agent, since it is relatively safe, cheap, and widely available. It reduces the risk of recurrent stroke within the acute phase of 2–4 weeks post-AIS if administered within 48 hours of onset (77, 78). A meta-analysis of 16 secondary prevention trials concluded that aspirin reduces the risk of recurrent ischemic stroke by 22% and has the strongest effect in the early weeks after AIS (79, 80). The P2Y12 inhibitor clopidogrel is another commonly used antiplatelet agent in AIS. The Clopidogrel with Aspirin in Acute Minor Stroke or Transient Ischemic Attack (CHANCE) trial, a study with primary Asian ethnicity, demonstrated a reduction of 90-day

stroke incidence after minor strokes (NIHSS < 4) or TIAs with the combination therapy aspirin and clopidogrel (dual antiplatelet therapy) for 21 days poststroke when compared with aspirin alone, without demonstrating an increase in hemorrhages (81). The American Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA (POINT) trial was able to reproduce those results in a more ethnically diverse cohort (82). Finally, cardioembolic strokes that account for up to 40% may warrant treatment with full anticoagulation to prevent recurrence. However, depending on the infarct size, full anticoagulation could result in hemorrhagic transformation in the immediate poststroke period. For these patients, an initial strategy of antiplatelet therapy bridging to full anticoagulation within 10–14 days of stroke is widely accepted and based on clinical trials that demonstrated the risk of stroke recurrence within this time frame is minimal (48, 83, 84). In certain patients with embolic strokes of undetermined source, long-term cardiac monitoring may be indicated to increase the yield of diagnosing paroxysmal atrial fibrillation (85).

Statins are the drug of choice for dyslipidemia, which is an important risk factor for atherosclerotic disease. In recent years, studies showed that statins have a pleiotropic effect beyond lowering cholesterol including being antithrombotic, anti-inflammatory, and endothelial protective (86). The The Stroke Prevention by Aggressive Reduction of Cholesterol Levels (SPARCL) clinical trial assessed the effect of statins on secondary stroke prevention and demonstrated that high-intensity atorvastatin reduces both fatal and nonfatal stroke recurrence with the highest effect in the carotid stenosis group. The study included patients with small-vessel occlusion, large vessel atherosclerosis, and unknown etiology excluding cardioembolic strokes (87). Recent clinical trials suggest that cholesterol low-density-lipoprotein level ~70 mg/dL is optional to decrease stroke recurrence (88). Although some studies showed an increased risk of ICH with statin therapy (89, 90), other pooled analyses failed to demonstrate that relationship (91, 92).

## CONCLUSIONS

Over the last few decades, multiple new innovations have introduced a new era of vascular neurology and included more patients for acute treatment, leading to improved outcome. Despite these groundbreaking changes, the constant decline in stroke mortality has slowed down and even reversed in several states of the United States (93). One of the reasons for this trend is the rising number of patients with stroke risk factors like diabetes, hypertension, and hyperlipidemia. In the future, the focus should shift more toward patient education and prevention in order to reduce the incidence of stroke leading to severe disability or death.

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