Diagnosis and Management of Acute Ischemic Stroke

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Abstract

Acute ischemic stroke (AIS) is among the leading causes of death and long-term disability. Intravenous tissue plasminogen activator has been the mainstay of acute therapy. Recently, several prospective randomized trials documented the value of endovascular revascularization in selected patients with large-vessel occlusion within the anterior circulation. This finding has led to a paradigm shift in the management of AIS, including wide adoption of noninvasive neuroimaging to assess vessel patency and tissue viability, with the supplemental and independent use of intravenous tissue plasminogen activator to improve clinical outcomes. In this article, we review the landmark studies on management of AIS and the current position on the diagnosis and management of AIS. The review also highlights the importance of early stabilization and prompt initiation of therapeutic interventions before, during, and after the diagnosis of AIS within and outside of the hospital.

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Acute ischemic stroke (AIS) is a medical emergency, affecting 795,000 people in the United States each year.[1] The global burden of AIS on society continues to rise with increasing incidence, in part due to increasing longevity. Since the 1990s, intravenous (IV) tissue plasminogen activator (IV tPA) has been the only evidence-based therapeutic option for improving outcomes for patients with AIS. Subsequently, intra-arterial thrombolysis (IAT) was tested in the Prolyse in Acute Cerebral Thromboembolism II (PROACT II) study, which found potential safety and efficacy of IAT for middle cerebral artery (MCA) occlusions treated within 6 hours.[2] Subsequently, the Interventional Management of Stroke (IMS) trial investigated the feasibility and safety of combined IV and intra-arterial therapy in AIS.[3] The ensuing years witnessed the evolution of endovascular procedures, from forcefully injecting thrombolytic agents or saline into the thrombus to mechanically disrupting the clot by microwires and microcatheters, to the advent of energy-emitting endovascular devices and percutaneous angioplasty. These advances led to the development of simple snare devices followed by US Food and Drug Administration approval of the first device for the indication of opening cerebral vessels, the Merci Retrieval System (Concentric Medical, Inc), and subsequently by suction catheters, intracranial stents, and stent retrievers. In parallel to this evolution, the design of AIS trials advanced, and the value of endovascular revascularization was clearly shown after the application of rigorous patient selection criteria. This advancement resulted in the second paradigm shift in AIS care since the initial approval of IV tPA. This shift was attributable partly to the efficacy of stent retrievers in clot extraction but largely to the appropriate selection of patients with salvageable brain tissue based on multimodal imaging. In this review, we provide a comprehensive review of current advances in the management of AIS.

This review is not intended to substitute for existing comprehensive clinical practice guidelines for the management of AIS, which are readily available.[4,5] Instead, we hope to provide physicians evaluating and treating patients with AIS with actionable and evidence-based advice. The current review is focused on the first 48 hours after onset of stroke symptoms, particularly the first few hours, as this represents the time when reduction of final infarct volume is most likely to be achieved.

PREHOSPITAL EVALUATION AND TRIAGE

Educating the public to recognize the symptoms and signs of acute stroke and use of urgent triage and treatment are essential to improve outcomes. This effort requires public service campaigns, emergency medical services (EMS), and development of systems of care for rapid transfer of patients to nearby stroke centers.

Prehospital assessment scales have been developed to identify acute stroke and severity, including the Los Angeles Prehospital Stroke Screen,[6] the Rapid Arterial Occlusion Evaluation scale,[7] and the Cincinnati Stroke Triage Assessment Tool.[8] None have shown to be superior to another in identifying large-vessel occlusion (LVO). The FAST acronym (face drooping, arm weakness, speech difficulty, time to call emergency services) has been endorsed by multiple professional organizations and has been the centerpiece of recent educational campaigns.[9] Calling EMS (by dialing 9-1-1 in the United States) when stroke is suspected must be emphasized because use of EMS is associated with faster arrival to the emergency department (ED) and higher rates of treatment with reperfusion therapies.[10] Training of dispatch personnel to recognize the urgency of stroke and the use of standardized stroke scales in the prehospital setting are also very important and may increase diagnostic accuracy.[11-13] Prearrival notification of the ED that a suspected stroke case is being transported has been shown to accelerate times to thrombolysis.[14] As useful as the FAST acronym is, it has considerable limitations, particularly with regard to posterior circulation and right hemispheric stroke symptoms (eg, hemianopia, diplopia, and neglect). Richer conversations regarding signs of stroke are warranted for patients at high risk.

Although the role of primary stroke centers (PSCs) has focused on prompt administration of IV tPA, the emergence of recent endovascular trials and mobile stroke units

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(MSUs) has initiated a debate about bypassing PSCs in patients with severe strokes caused by LVO and transferring these patients directly to comprehensive stroke centers (CSCs) with endovascular capabilities. The American Heart Association Mission: Lifeline Stroke's Severity-Based Stroke Triage Algorithm for EMS can be used to identify these patients.[15] Mobile stroke units are ambulances equipped with a computed tomography (CT) scanner, point-of-care laboratory, and telemedicine connection and have been reported to be safe and effective in reducing time to thrombolysis.[16] A randomized trial found a considerable reduction in the median time from alarm to therapy decision (35 minutes [interquartile range, 31-39 minutes] vs 76 minutes [interquartile range, 63-94 minutes]; $P<.0001$),[17] and treatment with IV tPA increased from 21% to 33%.[18] Further, transporting patients with severe symptoms directly to CSCs may lead to improved clinical outcomes.[19] In one study, 46% of the 52 candidates for transfer were diagnosed with intracerebral hemorrhage on portable CT, while 54% had AIS with need for thrombectomy. By establishing AIS diagnosis in the MSU, the PSC was bypassed and patients were taken directly to the CSC for further management.[20] Thus, the MSU saves critical time by allowing early triage of patients and differentiation between ischemic and hemorrhagic stroke in the prehospital setting. However, these units are expensive to purchase, maintain, and operate and remain available in only a few large urban areas. Therefore, bypassing PSCs could be detrimental because it will likely delay IV thrombolysis, and additional data are necessary before changing current models of triage based on "drip-and-ship" protocols (eg, initiation of IV thrombolysis at the closest ED followed by transfer to a CSC).

OUTSIDE HOSPITAL EVALUATION AND TRIAGE

Primary stroke centers provide timely assessment of patients and can initiate treatment with IV tPA. However, only 7.2% of patients with AIS receive IV tPA within 3 hours of symptom onset at local hospitals.[21,22] With the advent of telemedicine, patients with stroke can be evaluated promptly by stroke specialists remotely. Indeed, telestroke services are safe and comparable in quality to care provided face-to-face. The National Institutes of Health Stroke Scale (NIHSS), used to assess severity of deficit, can be performed remotely in a reproducible and accurate manner.[23-25] The implementation of telemedicine increases the use of IV tPA from 5% to 24% and shortens time to treatment (17 minutes vs 33 minutes; $P=.003$).[26,27] Despite established evidence supporting its use, barriers to telemedicine exist, including licensure and financial sustainability.

EMERGENCY DEPARTMENT EVALUATION

The first step is to verify that the patient is medically stable with a general examination focused on vital signs and the cardiovascular system. Comorbidities are common in this patient population, with most patients having a history of hypertension and about one-third having diabetes mellitus. Peripheral, coronary, and other arterial diseases are also common. The evaluating physician needs to be vigilant to other emergency conditions that can present with stroke. Ten percent of patients with type A aortic dissections present with stroke, and aortic dissection should be considered in patients with hemiparesis, widened mediastinum on chest radiography, elevated D-dimer level, and a systolic blood pressure difference between arms.[28] Observational studies have found that stroke risk increases 4 months before diagnosis of infective endocarditis.[29] In some instances, the elevated risk is due to occult infective endocarditis.

Every patient with suspected acute stroke should have a focused neurologic examination yielding an NIHSS score, which ranges from 0 (no obvious deficit) to 42 (quadriplegia and deep coma). The NIHSS is a structured and standardized neurologic examination of consciousness, vision, ocular, facial, and limb movement, coordination, sensation, language, and awareness. Online training and certification modules are available through the American Heart Association. Trained examiners should typically have an interobserver agreement within 1 point of each other when assessing the same patient. The score predicts 90-day functional outcomes after thrombolysis and LVO amenable to mechanical thrombectomy.[30] Stroke can be defined as mild, moderate, or severe on the basis of day 1 NIHSS scores of less than 6, 6 to 13, and greater

than 13 points, respectively, as these scores correlate well with hospital disposition.[31] A validated pediatric version of the NIHSS is also available.[32,33] However, the NIHSS is not a substitute for a full neurologic examination. Because of severity biases against nondominant MCA and posterior circulation strokes, the NIHSS may be unreliable in assessing right hemisphere strokes due to large-volume infarct compared with left hemisphere strokes.[34,35]

Most patients presenting with stroke symptoms have symptomatic cerebral infarction, but there are well-recognized stroke mimics, including postictal paralysis with or without aphasia, migrainous aura, subdural hematoma, functional deficits, hypoglycemic hemiparesis, and gliomatosis cerebri. Most stroke mimics cannot be diagnosed with certainty by noncontrast CT alone but may manifest on magnetic resonance imaging (MRI) or CT perfusion imaging (CTP).[36,37] Fortunately for both patients and physicians, IV thrombolysis is generally safe even if inadvertently given to patients with stroke mimics, with a 0.5% rate of intracerebral hemorrhage and a 0.3% rate of orolingual edema.[38]

Just as nonstroke events can be misclassified as stroke (mimics), strokes may also be misclassified as nonstroke events (chameleons). About 5% of cerebrovascular events are missed at initial ED presentation.[39] Common chameleons include acute mental status changes, syncope, hypertensive emergency, systemic infection, and acute coronary artery syndrome.[40] Younger patients and patients with mild neurologic symptoms or coma, fewer vascular risk factors, and other acute conditions are more likely to be misdiagnosed as having something else when they, in fact, have stroke.[41]

Immediate brain imaging is an essential first step in managing patients with stroke. The American College of Radiology considers either CT angiography (CTA) or magnetic resonance angiography (MRA) to be appropriate.[42] American Heart Association guidelines strongly recommend CTA or MRA for patients when endovascular therapy (EVT) is being contemplated to avoid sending patients to the catheter laboratory only to find out they have no clot to extract.[4] American Academy of Neurology guidelines support the superiority of diffusion-weighted imaging (DWI) over non–contrast-enhanced CT for diagnosing cerebral infarction; however, the majority of tissue exhibiting diffusion restriction will ultimately not be salvageable.[43] Thus, the prediction of patients with salvageable ischemic tissue cannot be estimated without supplementation by perfusion imaging. Additionally, 24-hour emergency MRI availability is limited in many centers.

NEURORADIOLOGY

Stroke therapy and neuroimaging have evolved concurrently to enable improved assessment of pretreatment risk-benefit profile, triage to appropriate therapy, and exclusion of stroke mimics. Noncontrast CT remains the only indispensable imaging modality for AIS work-up to exclude acute hemorrhage before proceeding with reperfusion therapies. Most EVT trials relied exclusively on CT and CTA in screening patients, and the Alberta Stroke Program Early CT Score (ASPECTS) was used to estimate the extension of the established infarction.

Computed tomographic perfusion imaging and DWI may offer important additional information for AIS triage. Multimodal CT protocols including CT, CTA, and CTP are increasingly available on an emergent basis in many centers. The main disadvantage of this approach is the time necessary to conduct this sequence of imaging. The development of automated software is helping ameliorate this issue. Although imaging times are longer when adding CTA/CTP, one study found an overall decrease in treatment times with the addition of CTA and CTP vs noncontrast CT alone, likely related to quick decision making and improved anatomic knowledge before EVT.[44] Magnetic resonance imaging can also be performed with MRA and magnetic resonance perfusion imaging. Additionally, DWI offers greater sensitivity and specificity for estimating volume of infarcted tissue.[45] Implementation of MRI in the AIS setting is more difficult because of many factors, such as 24-hour MRI availability and imaging times; however, many stroke centers do effectively use MRI for acute stroke triage.

Computed tomographic angiography and MRA allow rapid identification of LVO and clinically significant vascular disease.[46] In

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general, the performance and interpretation of CTA and MRA are less technically demanding than perfusion imaging and are effective for triaging patients for transfer to a CSC.

Computed tomographic perfusion imaging utilizes dynamic CT data consisting of multiple repeated head CT scans during the initial IV administration of iodinated contrast material. Based on the change in attenuation over time due to transiting contrast medium, several perfusion parameters are acquired, such as cerebral blood volume (CBV), cerebral blood flow (CBF), time to peak enhancement, and mean transit time (MTT). Both time to peak enhancement and MTT are quite sensitive to alterations in blood flow and can be used to identify areas of brain tissue potentially at risk.[47-49] Although there has been some debate on the use of these parameters in AIS, relative MTT has been found to be most predictive of at-risk tissue, whereas absolute CBV has been found to be most predictive of infarct core.[50] Areas of reduced CBF but increased or normal CBV predicts ischemic penumbra. Thresholds for irreversibly damaged tissue have been proposed as a CBV decrease to approximately 2 L/min, with MTT greater than 145%.[50] However, one should use absolute thresholds with some caution because they may vary considerably based on the software package used. Stroke practitioners should be familiar with published data utilizing the specific software package available in their institution. Volume of potentially salvageable tissue can be calculated as the volume of mismatch between decreased CBF and CBV.

Controversy has surrounded the use of perfusion imaging in AIS. Some major clinical trials, including the EXTEND-IA (Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-arterial) and SWIFT PRIME (Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke) studies, obtained CTP in a large subset of patients. Patients in these trials had a slightly higher frequency of functional independence compared with similar studies relying on noncontrast CT and CTA ASPECTS, such as REVASCAT (Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset) and ESCAPE (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times); however, this difference may be simply the result of the exclusion of patients with less favorable perfusion profiles.[51-54] Although the study design in these trials did not allow the true assessment of the role of CTP in predicting ischemic stroke outcomes, the results suggested that the subset of patients having a favorable perfusion profile by CTP may have better outcomes than a presumed mixed population. Unfortunately, because CTP was used as an enrollment criterion in these 2 trials, a difference in outcomes between patients with and without favorable perfusion profiles could not be determined. The CRISP (Computed Tomographic Perfusion to Predict Response to Recanalization in Ischemic Stroke Project) study also found better outcomes in patients after EVT who had a favorable perfusion profile compared with those with an unfavorable profile.[55] Yet, other studies have found conflicting results regarding the predictive power of CTP in finding no significant difference in clinical outcomes compared with noncontrast CT.[56,57] Two recent trials, the DAWN (DWI or CTP Assessment With Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo; ClinicalTrials.gov Identifier: NCT02142283) and DEFUSE (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke) 3 (ClinicalTrials.gov Identifier: NCT02586415) studies, identified patients with salvageable penumbra using clinical-radiographic mismatch criteria and found the benefits of delayed EVT independent of time windows (time of onset: 6-24 hours for DAWN and 6-16 hours for DEFUSE 3).[58,59]

Several barriers exist to effective implementation of perfusion imaging in acute stroke care. Differences in CT scanners result in variation in performance of CTP. Computed tomography scanners with smaller detector size limit the amount of brain that can be covered, while wide detector arrays allow whole-brain CTP. There is also variation in methodology for calculation of perfusion parameters. These

differences result in wide variability in CTP parameter estimation.[60,61] Although there is some agreement on the parameters that define favorable and unfavorable perfusion profiles, the selection criteria for intervention remain less clearly defined. Lastly, CT and magnetic resonance perfusion truly represent a simplistic measure of the complex metabolic changes occurring during brain ischemia, and a better understanding of how these measures relate to outcome is needed.[61,62] For instance, tissue with decreased CBF and increased MTT but maintained CBV may meet criteria for "penumbra" but may have already crossed a threshold at which cell death and infarction are inevitable despite recanalization.

INTRAVENOUS THROMBOLYSIS

Intravenous thrombolysis with alteplase became the first evidence-based short-term treatment for improving outcomes after AIS over 20 years ago.[63] Since then, this treatment has been confirmed to be effective within 4.5 hours of stroke onset in randomized controlled trials and through extensive experience across the globe.[64-66] Over time, it has also become clear that patients with some of the exclusion criteria from the original trials can safely receive thrombolysis.[67] Table 1 lists the current indications and contraindications for the use of IV alteplase for AIS.[5,67]

Intravenous alteplase (at a dose of 0.9 mg/kg, not to exceed 90 mg and with 10% of the dose given as a bolus and the rest as infusion over the following 60 minutes) increases the chances by one-third of recovery to independent function at 3 months when administered within 3 hours of stroke onset.[68] However, the therapeutic benefit decreases rapidly with time. Benefit is greatest in the first 90 minutes from symptom onset and no longer notable after 4.5 hours. Although outcomes are less favorable in very elderly patients, IV tPA is still beneficial in patients with preexisting cognitive or physical disabilities and in those with very severe neurologic deficits (likely related to proximal vessel occlusion by a larger clot).[66]

The most serious complication from IV tPA is intracranial hemorrhage (ICH). It often occurs in the area of infarction and is caused by reperfusion injury. Although most of these reperfusion hemorrhages are asymptomatic, they can sometimes provoke neurologic decline and, when severe, can be fatal. Hemorrhages remote from the infarction are less common but possible. The reported frequency of symptomatic ICH varies across studies depending on the definition used.[69] When symptomatic ICH is defined as radiologically proven hemorrhage with decline of 4 or more points on the NIHSS attributable to the hemorrhage, the risk is not higher than 2% to 3%.[69] Further, because these hemorrhages are more prone to occur in patients with large areas of ischemia, they typically make a bad situation worse, rather than harming patients who would have otherwise had a favorable prognosis.[70]

After IV tPA, patients need to be monitored in a dedicated stroke unit for 24 hours. Strict blood pressure control below 180/105 mm Hg is necessary, and antithrombotics should be avoided to reduce the risk of ICH. In case of neurologic worsening, CT should be repeated immediately. The presence of hemorrhage should prompt discontinuation of alteplase infusion if still ongoing. Cryoprecipitate or antifibrinolytics can be used to reverse the fibrinolytic effects of the drug,[71] although the benefit of these interventions remains unproven. In life-threatening cases, surgical evacuation of the hematoma can be considered. Orolingual angioedema is another uncommon complication of IV alteplase. It typically occurs shortly after alteplase administration, and the risk is increased in patients previously taking angiotensin-converting enzyme inhibitors and in those with involvement of the insular region.[72] Treatment consists of methylprednisolone (100-150 mg), diphenhydramine (25-50 mg), and an H_2 blocker. More severe cases may necessitate epinephrine (inhaled or subcutaneous) or even tracheal intubation.

Tenecteplase is a bioengineered variant of alteplase with longer half-life, greater fibrin specificity, and more resistance to plasminogen activator inhibitor 1. For many years, it has been the preferred thrombolytic agent for acute myocardial infarction. In one randomized trial, tenecteplase (0.4 mg/kg up to 40 mg as a single IV bolus) had safety and efficacy similar to the standard dose of alteplase among 1100 patients with AIS treated within 4.5

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TABLE 1. Indications and Contraindications for Intravenous Thrombolysis With Alteplase[a,b]

Indications
- Diagnosis of ischemic stroke causing a measurable disabling neurologic deficit
- Onset of symptoms <4.5 hours before beginning treatment[c]
- Age ≥18 years

Contraindications
- Severe head trauma in previous 3 months
- Symptoms suggestive of subarachnoid hemorrhage
- Previous ICH
- Intracranial/spinal surgery in previous 3 months
- Intracerebral neoplasm
- Infective endocarditis
- Aortic arch dissection
- Elevated blood pressure (systolic >185 mm Hg or diastolic >110 mm Hg) that cannot be lowered safely
- Active internal bleeding
- Acute bleeding diathesis, including but not limited to:
  - Platelet count <100,000/mm^3[d]
  - Heparin received within 48 hours with an elevated aPTT (>40 seconds)
  - Current use of treatment doses of low-molecular-weight heparin within the previous 24 hours (not applicable to DVT prophylactic dosages of low-molecular-weight heparin)
  - Current use of anticoagulant with INR >1.7 or PT >15 seconds[e]
  - Current use of direct thrombin inhibitors or direct factor Xa inhibitors[f]
- CT demonstrates infarction (hypodensity) >1/3 cerebral hemisphere
- CT demonstrates an acute ICH

Relative contraindications[g]
- Mild and nondisabling or rapidly improving stroke symptoms
- Very severe neurologic deficits (NIHSS score >25) within the 3- to 4.5-hour window
- Pregnancy
- Seizure at onset (consider alteplase if neurologic deficits are thought to be caused by a stroke)
- Arterial puncture at noncompressible site in previous 7 days
- Untreated intracranial arteriovenous malformation
- Untreated giant intracranial aneurysm
- Recent major surgery or serious trauma (within previous 14 days)
- Recent gastrointestinal or urinary tract hemorrhage (within previous 21 days)
- Ischemic stroke within previous 3 months
- Recent ST-elevation acute myocardial infarction (within previous 3 months)
- Blood glucose concentration <50 mg/dL (2.7 mmol/L) (consider IV alteplase if deficits still present after glucose normalization)

[a]aPTT = activated partial thromboplastin time; CT = computed tomography; DVT = deep venous thrombosis; ICH = intracranial hemorrhage; INR = international normalized ratio; IV = intravenous; NIHSS = National Institutes of Health Stroke Scale; PT = prothrombin time.

[b]For a detailed discussion of this topic, refer to the American Heart Association scientific statement on the rationale for inclusion and exclusion criteria for IV alteplase in acute ischemic stroke.[5,67]

[c]When uncertain, the time of onset should be considered the time when the patient was last known to be normal or at baseline neurologic condition.

[d]In patients without history of thrombocytopenia, treatment with IV tissue plasminogen activator (tPA) can be initiated before availability of platelet count but should be discontinued if platelet count is <100,000/mm^3.

[e]In patients without recent use of oral anticoagulants or heparin, treatment with IV tPA can be initiated before availability of coagulation test results but should be discontinued if INR is >1.7 or PT is abnormally elevated by local laboratory standards.

[f]Alteplase could be considered when results of laboratory tests such as aPTT, INR, ecarin clotting time, thrombin time, or direct factor Xa activity assays are normal or when the patient has not taken a dose of these anticoagulants for >48 hours and renal function is normal.

[g]Limited data and collective experience suggest that under some circumstances—with careful consideration and weighting of anticipated risk and benefit—patients may receive fibrinolytic therapy despite 1 or more relative contraindications. Consider risk to benefit of IV alteplase administration carefully if any of these relative contraindications are present.

From the American Heart Association.[5]

hours of symptom onset.[73] Although the results did not meet the superiority criterion, they may be sufficient to consider tenecteplase as a valid alternative to alteplase, particularly given the convenience of its administration as a single bolus. Yet, alteplase remains the only approved thrombolytic agent for treating AIS to date.

ENDOVASCULAR THROMBECTOMY

In 2015, EVT became standard of care after publication of the results of 5 prospective trials demonstrating its benefit in selected patients with AIS (Table 2).[51-54,59,74,75] Intravenous tPA administration continues to be a standard of care, and when given in parallel to EVT, it does not seem to raise safety concerns.[76] Patients eligible for IV tPA should begin receiving it regardless of decision for further neurovascular imaging or decision for EVT.[4,5,63,77-80] Patients ineligible for IV tPA received clear benefit from EVT over medical management alone.[53,54,74] Time to revascularization remains the most critical metric for improved clinical outcomes.[81] With every 1-minute improvement in door-to-treatment time, an average of 4.2 days of disability-free life is gained.[82] Patients younger than 55 years and with an NIHSS score of 15 or greater benefited even more—every 1-minute improvement in door-to-treatment time gained more than 7 days of disability-free life. This metric suggests that EVT is even more time dependent than IV tPA and was further confirmed by a meta-analysis of the 5 trials that had positive EVT findings.[83]

Patient Selection

Patient selection is very important, and results from recent trials showed better outcomes largely due to improved selection of patients for EVT, in addition to rapid neurovascular imaging,[76] the use of retrievable stents,[76,84] and rapid door-to-reperfusion time.[76] Patients with an NIHSS score greater than 6, or with a lower score and severe aphasia, should be considered for revascularization and should undergo vascular imaging to identify the occlusion site, proximal access, and distal collateral blood vessels, in addition to perfusion imaging to identify salvageable brain tissue. In patients with high creatinine levels, contrast medium intake can be reduced by using plain CT with ASPECTS score without CTP, and patients can be taken directly for cerebral angiography and possible EVT. Favorable imaging parameters include an ASPECTS score of 6 to 10 on noncontrast CT, a notable area of mismatch on CTP, MRP, and/or MRI with core infarct of less than 70 mL, and evidence of anterior circulation LVO with good collateral vessels on CTA.[85] Patients with these criteria should be considered for EVT without delay.

Endovascular Revascularization Techniques

Although common practices differ and the use of general vs local anesthesia has been debated, we prefer starting the endovascular procedure with local anesthesia and mild sedation. The head is secured in a head holder to prevent major movement, and patients can be converted to general anesthesia with intubation in case of emesis or extreme agitation. Endovascular access is obtained rapidly through the common femoral artery or, alternatively, through the radial or brachial arteries in patients with bilateral femoral occlusion. Selection of endovascular devices can be guided by CTA findings (eg, proximal vascular access, site and extent of the occlusion). After obtaining access, angiographic imaging is used to help navigate the vascular tree. Microcatheter and microwire are advanced past the occlusion site. Dual contrast injection from the microcatheter and proximal catheter are used to confirm the microcatheter position within the distal vessel and the proximal occlusion site. Stent retrievers are delivered through the microcatheter and are deployed across the occlusion site to engage the clot into the stent interstices. Alternatively, large suction catheters can be delivered to the proximal occlusion site to aspirate the thrombus without the use of a stent retriever.[86] We prefer retrieving these devices immediately proximal to the occlusion by withdrawing the device into a middle-sized catheter placed under suction. This step will likely prevent distal shower emboli from clot breakdown while pulling the clot against the blood flow, and the combination of aspiration and stent retrievers leads to remarkably high recanalization rates (Thrombolysis in Cerebral Infarction scale, 2b/3) of greater than 90%.[86-90]

It is worth mentioning that recent EVT trials treated patients with occlusions of the

TABLE 2. Summary of Major Randomized Controlled Trials of Endovascular Therapy in Acute Ischemic Stroke[a]

Variable	SYNTHESIS Expansion[75]	IMS III[3]	MR RESCUE[75]	MR CLEAN[74]	ESCAPE[54]	SWIFT PRIME[51]	EXTEND – IA[52]	REVASCAT[53]	DAWN[58]	DEFUSE-3[59]
Age (y)	18-80	18-82	18-85	≥18	≥18	18-80	≥18	18-85	≥18	18-90
NIHSS inclusion criteria	≤25	≥10	6-29	≥2	>5	8-29	None	≥6	≥10	≥6
Premorbid condition	mRS 0-1	mRS 0-2	mRS 0-2	None	Barthel index ≥90	mRS 0-1	mRS 0-1	mRS 0-1	mRS 0-1	mRS 0-2
IV tPA use in treatment arm (%)	0	100	47	87.1	72.7	100	100	68	4.7	11
Treatment arm	IA drug and/or device	IA drug and/or device + IV tPA	MERCI/ Penumbra ± IV tPA	IA UK/tPA/ device ± IV tPA	Stent retriever ± IV tPA	Stent retriever ± IV tPA	Stent retriever ± IV tPA	Stent retriever ± IV tPA	Trevo retriever ± IV tPA	Trevo Retriever/Solitaire revascularization device/Penumbra thrombectomy system ± IV tPA
Control arm	IV tPA	IV tPA	± IV tPA	± IV tPA	± IV tPA	± IV tPA	± IV tPA	± IV tPA	± IV tPA	± IV tPA
Pretreatment imaging and selection criteria	CT; no criteria	CT, CTA; no criteria	Multimodal CT/MR; no criteria	NCCT, CTA; no criteria	NCCT, mCTA; ASPECTS ≥6	NCCT with CTA and CTP; DWI with MRA and MRP; revised small core (ASPECTS >5)	NCCT with CTA and CTP; no criteria	NCCT with CTA; ASPECTS >7 (>5 DWI)	<1/3 MCA on CT/MRI; distal ICA and/or M1 occlusion on MRA/ CTA; CIM on MR-DWI or CTP-rCBF: 0-<21 cm^3 core infarct + NIHSS ≥10 + age ≥80 y; 0-<31 cm^3 core infarct + NIHSS ≥10 + age <80 y; 31-<51 cm^3 core infarct + NIHSS ≥20 + age <80 y	CTP/CTA or MR-DWI/ PWI/MRA; rapid target mismatch profile with core up to 70 mL
Median time from stroke onset to groin puncture (min)	225	208	381	260	200	224	210	269	60; randomization to puncture	28; randomization to puncture
Territory of vessel occlusion	Not required at randomization	ICA, M1, BA	ICA, M1 or M2	Distal ICA, M1, M2, A1	Distal ICA, M1, M1 equivalent	ICA, M1	ICA, M1, M2	ICA, M1	Distal ICA, M1, M2	ICA, M1
TICI 2b/3 (%)	Not reported	40	27	58.7	72.4	88.0	86.2	65.7	84 (modified TICI ≥2b); 72.6 (original TICI ≥2b); 10.4 (TICI 3)	78

[a]A1 = first segment of anterior cerebral artery; ASPECTS = Alberta Stroke Program Early Computed Tomography Score; BA = basilar artery; CIM = clinical imaging mismatch; CT = computed tomography; CTA = CT angiography; CTP = CT perfusion; DWI = diffusion-weighted imaging; IA = intra-arterial; ICA = internal carotid artery; IV tPA = intravenous tissue plasminogen activator; M1 = first segment of middle cerebral artery; M2 = second segment of middle cerebral artery; MCA = middle cerebral artery; mCTA = multiphasic CTA; MR = magnetic resonance; MRA = MR angiography; MRI = MR imaging; MRP = MR perfusion; mRS = modified Rankin scale; NCCT = noncontrast CT; NIHSS = National Institutes of Health Stroke Scale; PWI = perfusion-weighted imaging; rCBF = relative cerebral blood flow; TICI = Thrombolysis in Cerebral Infarction scale; UK = urokinase.

internal carotid artery (ICA) and M1 segment of the MCA, and there are several scenarios in which the role of EVT is not clear. M2 occlusions were treated in the MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in The Netherlands) and EXTEND-IA (Extending the Time for Thrombolysis in Emergency Neurological Deficits - Intra-Arterial) trials, and only the MR CLEAN study included A1 occlusions. No posterior cerebral artery occlusions were included in any of these trials. Current stent retriever devices are not designed for deployment in small vessels, and the safety and efficacy of other techniques, including microwire and microcatheter manipulation of the clot, use of small suction catheters, and intra-arterial tPA, are not clearly established. Recanalization of carotid occlusions is challenging, and ICA terminus occlusions have the worst outcomes given the large clot burden and risk of clot breakdown and migration of distal emboli into patent vessels, which can worsen the outcomes. However, EVT has a clear benefit in extracranial carotid occlusions and with cervical ICA and "tandem" intracranial occlusion.[91] In tandem occlusions, the distal occlusion is often the cause of the patient's symptoms; therefore, we favor revascularization of the distal occlusion first followed by the proximal cervical carotid occlusion. We also favor the use of proximal protection with balloon catheters during revascularization of cervical carotid occlusions because of the risk of clot breakdown and distal embolization to unaffected vessels.

EVT Outcomes

As endovascular techniques continue to evolve, neurologic outcomes from EVT continue to improve. Results from recent trials indicate that the number needed to treat for at least 1 grade improvement in modified Rankin scale (mRS) was only 2.6, while for functional independence the number was 5.1.[91] Further, no upper age limit for thrombectomy is recommended[85] as the differential benefit of thrombectomy compared with IV tPA was as great in those older than 80 years as in their younger counterparts.[85] Similarly, the mortality among patients older than 80 years was reduced from 40% to 20%.[91] Additionally, improved response after EVT is greater in patients with severe stroke.[3] However, a similar response across various NIHSS scores was demonstrated on an individual-level meta-analysis.[91]

In terms of long-term outcomes, reperfusion therapy for ischemic stroke, including IV alteplase and EVT, does not diminish over time.[92,93] In an extended follow-up evaluation for the MR CLEAN trial, positive results were maintained at 1 and 2 years.[94] Endovascular therapy in patients with AIS resulted in functional recovery, as measured on the mRS, that was similar to the originally reported results at 90 days. The mortality rate was lower with EVT than with conventional treatment, although this difference was not statistically significant, whereas at 90 days, the risk of death was similar in the 2 groups. The percentages of patients with mRS scores of 0 or 1 at 2 years were lower than the percentages at 90 days in both groups.

Extended Window for EVT

Evidence continues to emerge in support of benefits of EVT beyond the routine 3-, 6-, and 8-hour time windows when used in highly selected patients. The DAWN trial evaluated EVT in late-window and wake-up patients and hypothesized that Trevo (Stryker) thrombectomy plus medical management leads to superior functional outcomes at 90 days when EVT is initiated within 6 to 24 hours of symptom onset.[58] The trial enrolled 206 participants and demonstrated significant reduction in poststroke disability and improved functional independence at 90 days following EVT. For every 2 and 2.8 patients who underwent EVT, 1 additional patient had better scores for disability and functional independence, respectively.[58] The DEFUSE trial evaluated EVT within 6 to 16 hours of symptom onset for LVO within the anterior circulation. After review of the available DEFUSE 3 data by the Data Safety and Monitoring Board, the trial was terminated early in favor of EVT, and complete results were delivered recently at the international Stroke Conference 2018.[95] Although the time of symptom onset remains crucial in the management and outcomes of AIS,[96,97] results from these trials provide groundbreaking evidence supporting the use of imaging to identify salvageable brain, instead of using time from onset as

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www.mayoclinicproceedings.org

the sole determinant of the potential for reducing infarct volume, and opens new opportunities for extending the time for EVT even further.

POSTERIOR CIRCULATION/BASILAR ARTERY OCCLUSION

Basilar artery occlusion (BAO) is one of the most devastating neurologic conditions. It comprises only 1% of all stroke syndromes but has an exceptionally high morbidity and mortality (80%-90%) in the absence of treatment.[98] The time window for IV tPA is often extended beyond 4.5 hours because of its devastating nature and because 67% of the patients present more than 3 hours from symptoms onset.[99] Randomized trials of EVT have selected patients with LVO in anterior circulation, and there have been no well-designed trials to guide how to manage patients with BAO. Currently, a multicenter randomized trial with blinded outcome assessment (Endovascular Interventions versus Standard Medical Treatment [BEST]) is designed to compare the safety and efficacy of EVT in patients with BAO. A total of 344 patients with acute BAO within 8 hours of estimated occlusion time will be enrolled over 3 years and will be randomized 1:1 to standard medical therapy with or without EVT.[100]

Prior to the BEST study, the Australian Urokinase Stroke Trial was the only randomized controlled trial assessing the efficacy of IAT in BAO. Intra-arterial urokinase was tested in 8 patients with posterior circulation occlusion within 24 hours from symptom onset.[101] Although the study had insufficient power to draw statistically significant conclusions, the results favored the use of intra-arterial thrombolytics in patients with vertebrobasilar occlusions (VBO).[102] Good clinical outcome was seen with IAT (50%) when compared with placebo (12.5%).[101] Another study included 180 patients with acute VBO treated with IAT and reported complete recanalization in 55% and partial recanalization in 19%. A favorable pretreatment score (mRS, 3-4) was significantly correlated with good to moderate clinical outcome (mRS, 0-4) after recanalization.[103] Pretreatment mRS score, age, and coma duration of less than 4.5 hours strongly correlated with clinical outcome.[103] However, these studies failed to determine an appropriate time window to exclude the use of intra-arterial fibrinolysis.[102]

With the recent advancement in stent retrievers and aspiration systems, the use of EVT in VBOs will likely increase. One retrospective study compared the use of recent and older devices in acute BAO in 34 consecutive patients. By comparison, the recanalization rate (Thrombolysis in Cerebral Infarction scale, 2b/3) was higher (92.3% vs 23.8%; P=.0002) with a shorter mean procedure time (88±31 minutes vs 126±58 minutes; P=.04) using the Solitaire stent retriever and ADAPT technique than in patients treated with older devices.[104]

The Australian Urokinase Stroke Trial and other case series explored the use of IAT but were inconclusive about its efficacy. While the IMS III study included mostly ICA and M1 occlusions, only 4 patients with posterior circulation occlusion were enrolled, and there was no difference in outcome between the treatment and control groups.[3] Similarly, the Basilar Artery International Cooperation Study (BASICS) registry[105] had all the limitations of an observational study, and the results did not support the superiority of EVT (thrombolysis, mechanical thrombectomy, stenting, or a combination of these approaches) over IV thrombolysis. In the absence of compelling evidence to the contrary, management of patients with BAO should be guided by the severity of the symptoms, and it is reasonable to offer EVT to patients with severe symptoms, and patients with mild deficits can be treated with anticoagulation/antithrombotic treatment, in addition to IV tPA.[102]

MECHANISTIC EVALUATION OF STROKE

As soon as the patient is stabilized following a stroke, and in many instances even before that, it is important to investigate the stroke mechanism because it alters the therapy for secondary stroke prevention. To exclude cardioembolism, it is essential to diagnose persistent or intermittent atrial fibrillation (AF). All patients with AIS should undergo continuous electrocardiographic monitoring and careful review for evidence of AF. Even if no AF is detected in the hospital, prolonged outpatient monitoring should be done shortly after discharge with either mobile cardiac outpatient telemetry or an implantable loop recorder. Ultimately, AF may be detected in

nearly one-quarter of patients with stroke.[106] Echocardiography is often done, although the yield for treatment-altering findings is low in the absence of known or suspected cardiac pathology. For patients with nondisabling strokes, it is essential to diagnose ipsilateral high-grade cervical carotid artery stenosis, as endarterectomy is effective for preventing stroke.[107] If neither CTA nor MRA of the neck has been performed during the initial work-up, CTA, MRA, or duplex ultrasonography can be done to screen for stenosis.

MANAGEMENT OF MALIGNANT INFARCTION

Although most hemispheric infarctions reach their maximal swelling after 3 to 5 days, infarctions involving the entire MCA territory (with or without anterior cerebral artery territory involvement) can produce life-threatening swelling within the first 48 hours. These "malignant" infarctions demand treatment in the intensive care unit. Medical therapies (including osmotic agents, such as mannitol and hypertonic saline) are at best supportive or merely temporizing. Without decompressive surgery, the mortality in these cases exceeds 60% to 70%.[108]

Decompressive hemicraniectomy with dural expansion is very effective in reducing mortality in patients with malignant hemispheric brain infarctions.[108,109] However, functional outcomes after surgery are highly dependent on age and rehabilitation potential. In randomized trials, 55% of survivors aged 60 years or younger had regained the ability to walk, and 18% were functionally independent at 1 year.[108] However, the outcomes were much poorer among survivors older than 60 years (11% were able to walk, while none were functionally independent at 1 year).[109] Thus, clinicians should carefully discuss the expected postsurgical prognosis with patients and families before proceeding with the decompression, especially when contemplating the intervention for older patients. If surgery is pursued, it should ideally take place within the first 48 hours or very shortly after neurologic decline from swelling begins to ensue.

Large cerebellar infarctions—typically involving the posterior inferior cerebellar artery territory—can lead to death by occluding the fourth ventricle, causing obstructive hydrocephalus and brain stem compression. In such cases, emergency ventriculostomy and suboccipital craniectomy with dural expansion can save lives.[110] Many of these patients can ultimately regain good function. Although there is a clear correlation between the size of the cerebellar infarction and the risk of secondary neurologic decline from swelling, there is no accurate method to predict which patients will require surgical intervention, and therefore, close neurologic monitoring in the intensive care unit is indispensable.[111]

SUPPORTIVE CARE AND REHABILITATION PLANNING

Patients first need to be evaluated for airway compromise and risk of aspiration. Patients should be routinely placed on aspiration, deep venous thrombosis, fall, and seizure precautions. Once stable, the neurologist member of the stroke team should determine whether the patient needs long-term supportive care or short-term rehabilitation after discharge from the hospital. This usually requires additional expertise from physical and occupational therapy services and case management. There have been several recent large pragmatic trials that help to inform proper supportive care. A cluster-randomized trial found no differences in functional outcome from elevating the head of the bed vs keeping the patient supine.[112] A randomized trial of enteral feeding for those who cannot safely swallow did not demonstrate significant reduction in risk of death or poor outcome for early vs delayed feeding.[113] A single-blind randomized trial involving more than 2000 individuals found that very early mobilization (within 24 hours of stroke onset) is associated with poorer functional outcome than usual care.[114]

CONCLUSION

Acute stroke management has evolved tremendously over the years and will likely continue to improve with individualized patient care and careful selection criteria. In addition to IV tPA, EVT is now a standard of care in patients with LVO of the anterior circulation. Extending the therapeutic window to 24 hours has recently been established by the DAWN trial for selected patients based on imaging identification of salvageable brain tissue.

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Despite these paradigm shifts in stroke management, disability from AIS remains pervasive, and there is still need for developing criteria for revascularization of posterior circulation and BAOs. Improvements are also needed for developing systems in the prehospital and posthospitalization settings and for rapid transfer of patients to appropriate stroke centers for timely management.

Abbreviations and Acronyms: **AIS** = acute ischemic stroke; **AF** = atrial fibrillation; **ASPECTS** = Alberta Stroke Program Early CT Score; **BAO** = basilar artery occlusion; **CBF** = cerebral blood flow; **CBV** = cerebral blood volume; **CSC** = comprehensive stroke center; **CT** = computed tomography; **CTA** = CT angiography; **CTP** = CT perfusion imaging; **DAWN** = DWI or CTP Assessment With Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention With Trevo; **DEFUSE** = Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke; **DWI** = diffusion-weighted imaging; **ED** = emergency department; **EMS** = emergency medical services; **EVT** = endovascular therapy; **IAT** = intra-arterial thrombolysis; **ICA** = internal carotid artery; **ICH** = intracranial hemorrhage; **IMS** = Interventional Management of Stroke; **IV** = intravenous; **LVO** = large-vessel occlusion; **MCA** = middle cerebral artery; **MRA** = magnetic resonance angiography; **MR CLEAN** = Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in The Netherlands; **MRI** = magnetic resonance imaging; **mRS** = modified Rankin Scale; **MSU** = mobile stroke unit; **MTT** = mean transit time; **NIHSS** = National Institutes of Health Stroke Scale; **PSC** = primary stroke center; **tPA** = tissue plasminogen activator; **VBO** = vertebrobasilar occlusion

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The Thematic Reviews on Neurosciences will continue in an upcoming issue.

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