Chapter 1

Cerebrovascular disease: ischemic

Kevin M. Barrett and Thomas G. Brott

Introduction

Acute ischemic stroke is a medical emergency. Patients with suspected stroke require urgent evaluation to identify those who may be eligible for time-sensitive reperfusion therapies. Neurohospitalists are uniquely positioned to provide urgent assessment and time-sensitive therapies for patients with cerebrovascular emergencies. This chapter will review the practical aspects of acute stroke evaluation, evidence-based ischemic stroke treatment strategies, and secondary preventative strategies commonly initiated in the hospital.

Diagnosis of acute ischemic stroke

Bedside assessment

Stroke is a clinical diagnosis. A focused and systematic approach improves the likelihood of identifying patients with probable ischemic stroke and minimizes the risk of exposing patients with alternate diagnoses to potentially harmful treatment. Although the discussion that follows is presented sequentially, it is important to recognize that many elements of the stroke evaluation occur in parallel, depending on clinical circumstances or availability of resources.

The history should focus on establishing the time of symptom onset and identifying potential contraindications to acute stroke therapy (Table 1.1). When available, an eyewitness can be used to confirm the patient's reported time of symptom onset or provide the time of onset when the patient cannot. The use of cues (e.g. "before or after lunch?" or "before or after the evening news?") may be helpful in generating an estimated time of onset. In some circumstances, a precise time of symptom onset will prove impossible to determine and the line of questioning should then shift to identifying when the patient was last neurologically normal. For patients who awaken with symptoms, the time of onset becomes the time at which they went to sleep, assuming they were normal at that time. For patients with heralding stroke symptoms such as an antecedent transient ischemic attack, it is necessary to ensure complete resolution of symptoms before the clock can be "reset".

The nature of symptom onset should be obtained when possible. Symptoms that begin abruptly suggest a vascular etiology, whereas symptoms that begin in one region and gradually spread to involve other areas may suggest an alternate etiology (i.e. migraine or seizure). Inquiry should be made regarding risk factors for vascular disease, as well as any history of seizures, migraine, insulin use, or drug abuse that may suggest another cause for the patient's symptoms. Accompanying symptoms, particularly headache, warrant further investigation. Ictal, or so-called "thunderclap", headache should alert the clinician to the possibility of subarachnoid hemorrhage. Small bleeds or sentinel leaks from intracranial aneurysms may not be evident on CT scan. Further evaluation with lumbar puncture to exclude the presence of blood in the subarachnoid space may be warranted when clinical suspicion remains high [1].

The initial evaluation of the potential stroke patient often occurs in a high-acuity area. Medical personnel responsible for establishing i.v. access, initiating cardiorespiratory monitoring, performing blood draws, and performing electrocardiography compete for the patient's attention. Additionally, the presence of aphasia or neglect may limit the patient's ability to provide accurate information. To the neurohospitalist performing the initial assessment, these activities pose significant challenges. Despite such

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Table 1.1. Important historical information in the suspected stroke patient

History of the present illness	Time of symptom onset Evolution of symptoms Convulsion or loss of consciousness at onset Headache Chest pain at onset
Past medical history	Prior intracerebral hemorrhage Recent stroke Recent head trauma or loss of consciousness Recent myocardial infarction
Past surgical history	Recent surgical procedures Arterial puncture
Review of systems	Gastrointestinal or genitourinary bleeding
Medications	Anticoagulant therapy

barriers, critical elements of the history may be obtained indirectly. Emergency medical personnel can provide important information regarding vital signs and blood glucose levels obtained in the field. Observations regarding level of consciousness, initial severity of deficits, and the presence of bowel or bladder incontinence at the scene provide useful clues to the etiology and evolution of the presenting symptoms. Reaching a family member by telephone may be necessary if no one is immediately available. In certain circumstances, attempting to reach the patient's primary care provider may prove useful. Documentation of prior stroke, TIA, or other neurological morbidity in past medical records is valuable. Chronic or previously resolved deficits may potentially confound interpretation of neurological examination findings in the acute setting. Examination of medication bottles, if they accompany the patient, may provide clues to co-existing medical conditions or anticoagulant use.

As in any critically ill patient, the first priority is assessment and stabilization of the patient's airway, breathing, and circulation. Findings on general physical examination may facilitate stroke diagnosis and influence treatment decisions. When performing the general examination, attention should be focused on the cardiovascular system. The presence of a cervical bruit, cardiac murmur, or irregular heart rhythm may provide an important clue to the underlying stroke mechanism. Unequal extremity pulses may suggest aortic dissection or the presence of concomitant peripheral arterial disease. Funduscopic examination may reveal signs of chronic hypertensive arterial disease or endocarditis. Signs of head or neck trauma (e.g. contusions, lacerations) should prompt consideration of occult cervical spine injury. Other findings, such as rales on chest examination or bilateral asterixis, may suggest an alternate explanation (i.e. pneumonia or metabolic encephalopathy) for the patient's symptoms.

The neurological examination should focus on identifying signs of lateralized hemispheric or brainstem dysfunction consistent with stroke. Commonly encountered ischemic stroke syndromes are outlined in Table 1.2. The site of vascular occlusion and the extent of collateral flow dictate whether a complete or partial syndrome is present. The National Institutes of Health Stroke Scale (NIHSS) is a validated scale that has gained widespread acceptance as a standard clinical assessment tool. It assesses level of consciousness, ocular motility, facial and limb strength, sensory function, coordination, language, speech, and attention (Table 1.3). The NIHSS may be performed rapidly, measures stroke severity, and predicts short-term and long-term neurological outcomes [2]. Additionally, NIHSS severity may provide information regarding the likelihood of identifying a large-vessel occlusion with vascular imaging [3].

The NIHSS has important limitations. It does not include a detailed assessment of the cranial nerves, and relatively low scores may occur in patients with disabling brainstem or cerebellar infarction [4]. Likewise, milder deficits caused by focal cerebral ischemia, such as impaired hand dexterity or fine finger movements, may escape detection if not specifically tested. Stroke severity may not be accurately reflected in non-dominant hemisphere syndromes as compared to dominant hemisphere strokes [5], and a reliable score is often difficult to obtain in patients with encephalopathy or cognitive dysfunction. Clinically important changes on serial examination may not be reflected as a measurable change on the NIHSS. Finally, one should recognize that the presence of an abnormality on the NIHSS does not support or refute a diagnosis of stroke. As discussed below, many other conditions may cause stroke-like symptoms and NIHSS abnormalities. A thorough clinical evaluation often includes the NIHSS and a comprehensive neurological examination.

Table 1.2. Common ischemic stroke syndromes

Arterial distribution	Common signs
Left middle cerebral artery	Aphasia Right hemiparesis/ hemisensory disturbance Right homonymous hemianopia Left head and gaze preference
Right middle cerebral artery	Left hemispatial neglect Left hemiparesis/hemisensory disturbance Left homonymous hemianopia Right head and gaze preference Anosognosia
Left posterior cerebral artery	Right visual field defect Impaired reading (alexia without agraphia) Poor color naming Right hemisensory disturbance
Right posterior cerebral artery	Left visual field defect Visual neglect Left hemisensory disturbance
Vertebrobasilar	Vertigo, nausea Diplopia Quadriparesis Crossed motor or sensory findings (ipsilateral face, contralateral body) Truncal or limb ataxia Visual loss/dimming Impaired consciousness
Penetrating artery (i.e. lacunar syndromes) (A) Internal capsule/ corona radiata (B) Ventral pons (C) Thalamus	(A, B) Contralateral hemiparesis alone (pure motor stroke) OR contralateral hemiparesis + ataxia out of proportion to weakness (ataxic-hemiparesis); no cortical signs (C) Contralateral sensory loss alone (pure sensory stroke); no cortical signs

Stroke mimics and chameleons

When acute ischemic stroke is suspected, it is crucial to consider and to exclude alternative diagnoses, especially intracranial hemorrhage. Many conditions, including systemic abnormalities and other nervous system diseases, present with focal neurological

Table 1.3. National Institutes of Health Stroke Scale*

Category	Scale definition
1a. Level of consciousness	0 = Alert 1 = Not alert, arousable 2 = Not alert, obtunded 3 = Unresponsive
1b. Questions	0 = Answers both correctly 1 = Answers one correctly 2 = Answers neither correctly
1c. Commands	0 = Performs both tasks correctly 1 = Performs one task correctly 2 = Performs neither task
2. Gaze	0 = Normal 1 = Partial gaze palsy 2 = Total gaze palsy
3. Visual fields	0 = No visual loss 1 = Partial hemianopsia 2 = Complete hemianopsia 3 = Bilateral hemianopsia
4. Facial palsy	0 = Normal 1 = Minor paralysis 2 = Partial paralysis 3 = Complete paralysis
5a. Left motor arm	0 = No drift 1 = Drift before 10 s 2 = Falls before 10 s 3 = No effort against gravity 4 = No movement
5b. Right motor arm	0 = No drift 1 = Drift before 10 s 2 = Falls before 10 s 3 = No effort against gravity 4 = No movement
6a. Left motor leg	0 = No drift 1 = Drift before 5 s 2 = Falls before 5 s 3 = No effort against gravity 4 = No movement
6b. Right motor leg	0 = No drift 1 = Drift before 5 s 2 = Falls before 5 s 3 = No effort against gravity 4 = No movement
7. Ataxia	0 = Absent 1 = One limb 2 = Two limbs

Table 1.3. (*cont.*)

Category	Scale definition
8. Sensory	0 = Normal 1 = Mild loss 2 = Severe loss
9. Language	0 = Normal 1 = Mild aphasia 2 = Severe aphasia 3 = Mute or global aphasia
10. Dysarthria	0 = Normal 1 = Mild 2 = Severe
11. Extinction/ inattention	0 = Normal 1 = Mild 2 = Severe

* The full NIHSS with instructions and scoring sheet is available online at www.ninds.nih.gov/doctors/NIH_Stroke_Scale.pdf.

Reprinted with permission from Adams HP Jr, del Zoppo G, Alberts MJ, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/ American Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists [published errata appears in Stroke 2007;38(6): e38 and Stroke 2007;38(9):e96]. Stroke 2007;38(6):1655–1711.

Data from National Institute of Neurological Disorders and Stroke. [accessed 28 July 2008] Available at www.ninds.nih.gov/doctors/ NIH_Stroke_Scale.pdf.

deficits that "mimic" acute ischemic stroke. Table 1.4 lists commonly encountered stroke mimics. Some stroke mimics may be discovered early during the course of evaluation (e.g. hypoglycemia), but others may require more extensive investigation and/or neuroimaging. The history and examination help to determine the probability of a stroke mimic as the cause of neurological dysfunction. Distinguishing features of some stroke mimics are highlighted in Table 1.5.

A recent prospective study of more than 300 patients who presented to an urban teaching hospital with suspected stroke found mimics in 31% at the time of final diagnosis [6]. The most frequent mimics were post-ictal deficits (21%), sepsis (13%), and toxic-metabolic disturbances (11%). Seventy-five percent of mimics in the study were neurological disorders, and 42% of patients with a mimic had experienced a previous stroke. Eight variables independently associated with a correct diagnosis were

Table 1.4. Common acute stroke mimics

Post-ictal deficits (Todd paralysis)
Hypoglycemia
Migraine (hemiplegic, with aura)
Hypertensive encephalopathy
Reactivation of prior deficits
Mass lesions
Subarachnoid hemorrhage
Peripheral vestibulopathy
Conversion reaction

Table 1.5. Characteristics of common stroke mimics

Diagnosis	Comments
Seizure (post-ictal)	Focal deficits probably caused by seizure-induced neuronal dysfunction (reversible). May occur with simple partial or generalized seizures. Clinical seizure often unwitnessed or unrecognized. Spontaneous resolution over hours (may last up to 48 hours).
Hypoglycemia	Aphasia or hemiplegia may be present. Variable drowsiness or obtundation. Blood glucose usually < 45 mg/dL. Resolution of symptoms (immediate→ hours) with i.v. glucose.
Metabolic encephalopathy	Etiologies include hyperosmolar hyperglycemia, hyponatremia, hepatic encephalopathy. May be associated with altered level of consciousness, poor attention, disorientation (e.g. delirium) asterixis.
Conversion reaction	Diagnosis of exclusion. Conversion disorder most common psychiatric diagnosis. Comorbid psychiatric problems common. Paresis, paralysis, and movement disorders common.
Reactivation of prior deficits	Imaging evidence or history of remote stroke is present. Previous deficit may have resolved completely.

identified. The most powerful predictors of an accurate stroke diagnosis were "definite history of focal neurological symptoms" (odds ratio (OR) 7.21; 95% CI 2.48–20.93) and an NIHSS score greater than 10 (OR 7.23; 95% CI 2.18–24.05). In patients with known cognitive impairment, the likelihood of having a stroke was markedly reduced (OR 0.33; 95% CI 0.14–0.76). While studies such as these improve our general understanding of the frequency and nature of stroke mimics, the results are less applicable to individual patients. As emphasized previously, the diagnosis of stroke is based on a composite of information obtained from the history and the pattern of findings on physical examination. A single symptom or sign cannot be used to rule in or rule out the diagnosis [7].

The neurohospitalist should also be aware of atypical clinical presentations of stroke. The term stroke "chameleon" has been aptly used to describe an atypical stroke presentation that appears to mimic another disease process [8]. These patients may not be triaged into acute stroke pathways and, therefore, may be at higher risk of misdiagnosis. The clinician should suspect such problems when symptom onset is abrupt or occurs in patients with risk factors for cerebrovascular disease. A small proportion of patients with stroke may present with symptoms suggestive of an acute confusional state (e.g. delirium). While encephalopathy typically reflects diffuse hemispheric dysfunction, a "pseudo-encephalopathy" may occur with focal cerebral ischemia involving the limbic cortex or orbitofrontal regions. "Confusion" may also be reported in patients with fluent aphasia or neglect syndromes without accompanying motor deficits. Systematic neurological examination should identify these focal features and increase the clinical suspicion of stroke. Likewise, examination of visual fields will avoid overlooking patients with cortical blindness or visual neglect syndromes. Chest pain or discomfort mimicking myocardial ischemia has been reported in patients with infarction of the thalamus, corona radiata, or lateral medulla [9]. In some of these patients the sensory symptoms were part of a more extensive stroke syndrome, but the clinician should be aware of this possibility. Distal arm paresis with patterns of weakness conforming to a peripheral nerve (i.e. radial or ulnar) distribution may result from small cortical infarctions of the motor cortex [10]. Again, abrupt onset and the presence of vascular risk-factors should alert the astute clinician.

Ancillary testing

Laboratory and cardiac evaluation supplement the clinical impression derived from the bedside assessment. Some conditions that may present with stroke-like symptoms may be identified based on laboratory results (e.g. hypoglycemia). In addition, abnormal laboratory values may exclude patients from receiving thrombolytic therapy. Routine laboratory testing of blood glucose, electrolytes, complete blood count, prothrombin time, activated partial thromboplastin time, International Normalized Ratio, and renal function is recommended [11]. Testing for stool occult blood is not routinely recommended unless an indication exists (e.g. melena or hematochezia).

Cardiac abnormalities are common in patients with stroke. Serum troponin and a 12-lead electrocardiogram are recommended for all stroke patients. Myocardial infarction and atrial fibrillation are common causes of cardioembolism. Stroke symptoms such as aphasia may confound the clinical presentation of acute coronary syndrome. The utility of routine chest radiography as part of the acute stroke evaluation is limited and is currently not routinely recommended [12]. There is no role for routine CSF examination, unless warranted by the presence of sudden, severe headache concerning for subarachnoid hemorrhage. Urine toxicology screen, blood alcohol level, arterial blood gas, or testing for βHCG may be indicated depending on the clinical setting such as stroke with altered sensorium or stroke in a woman of childbearing age.

Neuroimaging

Brain imaging is the only reliable means to differentiate between ischemic and hemorrhagic stroke and is mandatory prior to administration of thrombolytic therapy [13,14]. Non-contrast head CT is the diagnostic standard in most centers given its widespread availability, low cost, and sensitivity to intracranial hemorrhage. However, the sensitivity of non-contrast head CT for the diagnosis of ischemic stroke within 6 hours of symptom onset is estimated to be between 40 and 60% [15]. In the acute setting, early ischemic changes such as loss of differentiation of the gray-white matter interface, particularly in the region of the insular cortex or the lentiform nucleus or sulcal effacement, may be apparent on CT (Fig. 1.1). Whether these changes are present in the minutes to hours after symptom onset is probably related to the

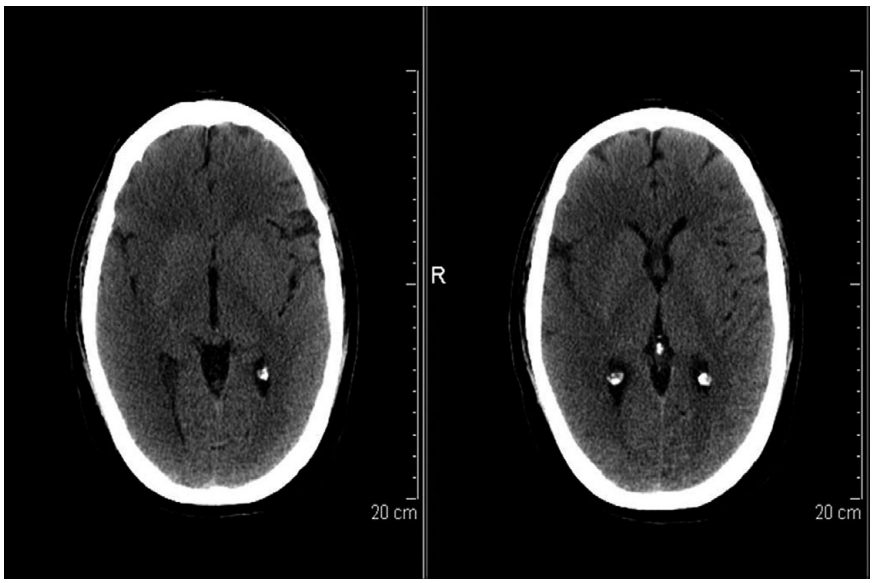

Fig. 1.1. Non-contrast head CT sequences from a 59-year-old woman with abrupt onset of slurred speech and left-sided weakness. Within the distribution of the right MCA there is a large area of subtle hypodensity with the loss of gray-white interface and loss of the insular ribbon consistent with an evolving right MCA infarction. Effacement of the cortical sulci is also seen consistent with early cytotoxic edema.

severity and extent of ischemia, collateral circulation, and presence of large vessel occlusion.

The appearance of ischemic changes on CT evolves with the duration of focal ischemia. Within 12 to 24 hours, an indistinct area of low density becomes apparent in the affected vascular distribution. After 24 hours, the ischemic region becomes increasingly hypodense and better circumscribed. Mass effect develops and results in sulcal asymmetry or ventricular distortion. The presence of a clearly delineated area of hypodensity with associated mass effect should, therefore, prompt reassessment of the time of symptom onset in patients thought to be eligible for thrombolytic therapy, as distinct hypodensity is inconsistent with focal cerebral ischemia of less than 3 hours. Other processes that can result in a distinct hypodensity include primary or metastatic cancer and contusion. It is important to look for subtle evidence of crossing of vascular territories, intralesional calcifications, or involvement of cortex, particularly if the lesion has a mesial temporal or frontopolar location. Bitemporal lesions from herpes simplex encephalitis can sometimes be mistaken for top-of-the basilar syndrome infarcts. Patients with HSV often have fever at presentation, unlike patients with acute ischemic stroke.

Evaluation of patients with acute stroke with MRI has clear advantages. Compared to CT, MRI with diffusion-weighted imaging (DWI) sequences is more sensitive for acute cerebral ischemia and improves diagnostic accuracy [16]. DWI may detect abnormalities within minutes after onset of cerebral ischemia [17] and delineates the location, size, and extent of hyperacute ischemia. MRI better evaluates the posterior fossa and improves visualization of small cortical infarctions. A recent systematic review suggests that DWI is accurate and superior to CT for the diagnosis of acute ischemic stroke [18]. The sensitivity of DWI is estimated to be between 80 and 90% in a general sample of patients evaluated for possible stroke (Fig. 1.2). False-negative DWI in ischemic stroke may occur with small hemispheric or brainstem stroke or when performed very early after symptom onset. Advances in technology such as higher field strength magnets and smaller axial slice thickness may overcome these limitations in the future.

Historical concerns about the ability of MRI to identify acute intracerebral hemorrhage have been addressed by several studies. Conventional T1- and T2-weighted MRI pulse sequences are able to identify subacute and chronic blood, but they are less sensitive for parenchymal hemorrhage during the first 6 hours after symptom onset. Susceptibility-weighted MRI, or gradient echo (GRE), sequences have improved sensitivity for recently extravasated blood products [19]. A prospective study of MRI and CT performed within 6 hours of stroke symptom onset demonstrated that the accuracy of GRE sequences for acute hemorrhage is equal to that of CT [20]. A smaller multicenter study found a similarly high

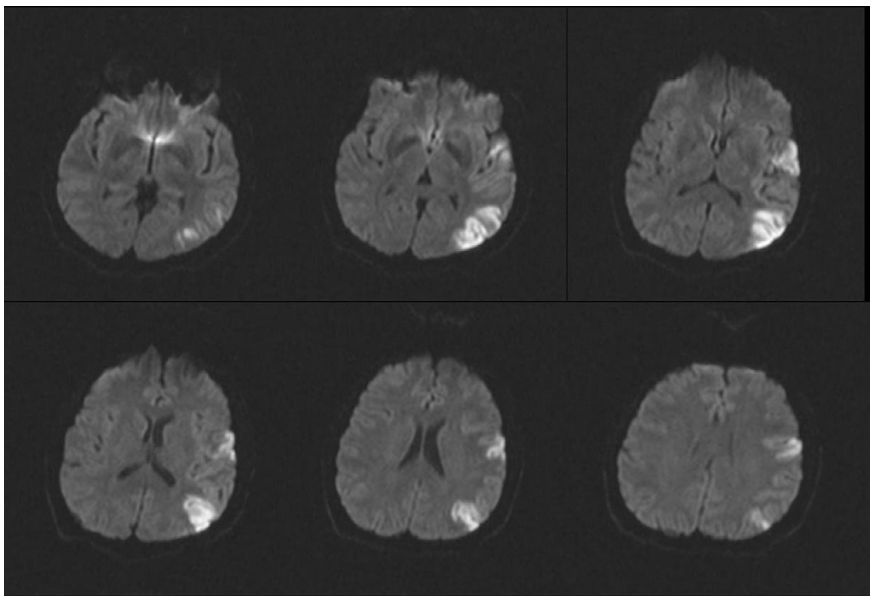

Fig. 1.2. Diffusion-weighted brain MRI sequences from a 39-year-old man with speech difficulty. The examination was remarkable for effortful speech, impaired verbal comprehension, and the inability to repeat, name, read, or write. The hyperintensity in the posterior-inferior left frontal lobe, adjacent superior left temporal lobe, and posterior parietal region is consistent with acute ischemic stroke.

accuracy of GRE for identification of acute intracerebral hemorrhage [21].

Some centers have developed extensive experience with MRI in acute stroke and have adopted the use of MRI protocols for routine evaluation of patients with stroke [22].

Many emergency departments lack the resources necessary to perform emergency MRI. The costs of the technology, including around-the-clock technician support, are prohibitive for many centers and have limited widespread implementation. Abbreviated stroke MRI protocols have been developed to address concerns about additional time needed to acquire MRI images compared to CT. This issue is important given the association between time to initiation of thrombolytic therapy and likelihood of an excellent neurological outcome [23]. MRI is contraindicated in patients with pacemakers or other metallic hardware and is further limited by its susceptibility to motion artifact in agitated patients.

Treatment of acute ischemic stroke

Intravenous thrombolysis: 0–3 hours

Intravenous recombinant tissue-type plasminogen activator (rtPA) is the only FDA-approved treatment for acute ischemic stroke. Approval was based on the results of the National Institute of Neurological Disorders and Stroke (NINDS) rtPA stroke study, which randomized 624 patients with acute ischemic stroke within 3 hours of symptom onset to treatment with either placebo or intravenous rtPA [24]. Favorable outcomes at three months were achieved in the 31–50% of patients treated with rtPA compared to 20–38% of patients in the placebo arm. This difference was statistically and clinically significant. Patients treated within 90 minutes of onset achieved better outcomes than those who were treated between 91 and 180 minutes, although there was still benefit. The benefit persisted when outcomes were reassessed at 12 months [25]. The major risk of treatment was symptomatic intracranial hemorrhage, which occurred significantly more frequently in the treatment group (6.4%) within 36 hours compared to the placebo group (0.6%). There was no significant difference in 3-month mortality between the treatment group (17%) and the placebo group (21%). The safety and efficacy of rtPA in routine clinical use have been subsequently confirmed in a large cohort of patients [26]. Based on these data, rtPA (0.9 mg/kg, maximum dose 90 mg) is recommended for carefully selected acute ischemic stroke patients. Intravenous rtPA is infused over 60 minutes, with 10% of the dose given as an initial bolus over one minute.

The exclusionary criteria for treatment with rtPA within 3 hours of symptom onset are modeled on the original eligibility criteria used in the NINDS study protocol [11] (Table 1.6). Initiating treatment

Table 1.6. Exclusion criteria for intravenous thrombolysis

Exclusion criteria for intravenous rtPA < 3 hours after symptom onset[†]	CT or MRI evidence of intracranial hemorrhage Rapidly resolving or minor and isolated deficit Seizure with post-ictal deficits Symptoms suggestive of subarachnoid hemorrhage History of previous intracranial hemorrhage Head trauma or prior stroke in previous 3 months Myocardial infarction in previous 3 months Gastrointestinal or urinary tract hemorrhage in previous 21 days Major surgery in previous 14 days Arterial puncture at a non-compressible site in previous 7 days Blood pressure persistently elevated >185 mmHg systolic or >110 mmHg diastolic Active bleeding or acute trauma (fracture) on examination International Normalized Ratio (INR) > 1.7 Received heparin within 48 hours and aPTT elevated Platelet count ≤ 100 000 mm^3 Blood glucose ≤ 50 mg/dL CT evidence of multilobar infarction (hypodensity > 1/3 cerebral hemisphere) Caution in severely affected, obtunded or comatose patients
Additional exclusion criteria for intravenous rtPA 3–4.5 hours	>80 years old Oral anticoagulant use (regardless of INR value) Baseline NIHSS > 25 History of stroke and diabetes

[†] Table adapted from Adams et al. 2007 [11].

with rtPA prior to obtaining results of platelet or coagulation studies is feasible and safe [27] and can be considered unless a bleeding disorder or thrombocytopenia is suspected [11]. Early ischemic changes (loss of gray-white differentiation, sulcal effacement) were not independently associated with adverse outcome in the NINDS rtPA trial and should not be used as the singular reason to preclude thrombolytic therapy in otherwise eligible patients [28]. Clearly evident hypodensity involving more than a third of the middle cerebral artery territory should prompt reconsideration of the reported time of symptom onset. Seizures are a relative contraindication for rtPA treatment given their tendency to mimic the symptoms of stroke. However, seizures are estimated to occur in up to 6% of patients at the time of ischemic stroke onset [29]. Case series suggest that thrombolysis can be administered to patients with seizures at the time of presentation when advanced neuroimaging techniques such as CT perfusion or diffusion/perfusion-weighted MRI suggest that neurological deficits are due cerebral ischemia rather than a post-ictal state [29,30].

Written informed consent is not mandatory prior to administration of rtPA for acute ischemic stroke [11]. However, treating physicians are obligated to inform the patient and/or family members regarding the rationale, risks, benefits, and alternatives to treatment with rtPA [31]. Placement of invasive devices such as nasogastric tubes, indwelling bladder catheters, and intra-arterial catheters should be delayed when possible in patients receiving rtPA. Antiplatelet and anticoagulant medications should not be administered until 24 hours after rtPA treatment. A follow-up CT scan at 24 hours is recommended to assess intracranial hemorrhage prior to initiation of anti-thrombotic therapy for secondary prevention [11].

When treatment with rtPA is initiated, frequent neurological assessments and blood pressure measurements should be performed every 15 minutes during the rtPA infusion, every 30 minutes for the next 6 hours, then hourly until 24 hours after treatment. This level of monitoring is best achieved in an intensive care unit or stroke unit with high nurse-to-patient ratios and nurses specifically trained and

experienced in standard neurological assessment tools such as the NIHSS and the Glasgow Coma Scale. Severe headache, acute hypertension, emergence of worsening or a new neurological deficit, nausea or vomiting, or depressed level of consciousness should raise the clinical suspicion for intracranial hemorrhage. If the rtPA infusion is ongoing when these signs or symptoms emerge, the infusion should be stopped immediately, followed by emergency non-contrast head CT to evaluate for symptomatic intracranial hemorrhage.

Most symptomatic intracerebral hemorrhages occur within 24–36 hours after initiation of treatment [32]. Hemorrhagic transformation occurs when there is extravasation of blood into the brain parenchyma after ischemic alteration of the blood–brain barrier. Several clinical, biological, and imaging predictors of intracerebral hemorrhage have been studied. Advanced age [33], baseline stroke severity as measured by the NIHSS [34], hypertension [35], and hyperglycemia [36] have been identified as important clinical factors. Studies of an association between intracerebral hemorrhage and serum levels of biomarkers such as matrix metalloproteinase-9, cellular fibronectin, and plasminogen activator inhibitor-1 have yielded conflicting or inconclusive results. Routine measurement of these markers has not been incorporated into clinical practice [32]. Further study is needed to clarify the predictive value of baseline neuroimaging parameters such as diffusion-weighted imaging infarct volume and semi-quantitative measurements of cerebral perfusion.

The rapid clinical assessment and interpretation of neuroimaging studies necessary to provide thrombolytic therapy within a short time window has raised concern about administering rtPA to patients with non-stroke diagnoses [37]. Between 3% and 7% of patients who receive systemic thrombolysis for acute stroke are ultimately found to have a stroke mimic [38,39]. In a consecutive series of 69 patients who received intravenous rtPA and were ultimately diagnosed with a stroke mimic, there were no instances of symptomatic or systemic hemorrhage despite a range of non-stroke diagnoses [40]. These data suggest that rtPA can be safely administered to patients with non-stroke diagnoses. Therefore, delaying initiation of therapy to obtain additional diagnostic testing when alternate etiologies are being considered may not be warranted.

Intravenous thrombolysis: 3–4.5 hours

The third European Cooperative Acute Stroke Study (ECASS III) randomized patients to receive either 0.9 mg/kg rtPA ($n = 418$) or placebo ($n = 403$) between 3 and 4.5 hours after acute ischemic stroke onset [41]. Efficacy was assessed with the modified Rankin scale at 90 days and dichotomized as a favorable (score of 0 or 1) or an unfavorable clinical outcome (score of 2–6). Symptomatic intracranial hemorrhage was defined as clinical deterioration by more than a four-point increase in NIHSS score or death.

In contrast to the NINDS rtPA trial, ECASS III excluded patients with age greater than 80 years, severe stroke (NIHSS > 25), and those with history of diabetes and prior stroke.

Treatment with rtPA was significantly associated with a favorable outcome at 3 months (OR 1.34; 95% CI 1.02–1.76). Compared to placebo, the absolute increase in favorable outcome for the treatment group was 7.2% (52.4% vs. 45.2%, $P = 0.04$). The number needed to treat was 14. Symptomatic intracranial hemorrhage was significantly more frequent in the treatment group (2.4% vs. 0.2%, $P = 0.008$). Death was similar for both groups with a non-significant trend favoring the rtPA group (7.7% vs. 8.4%, $P = 0.68$).

Based on these results, administration of rtPA to eligible acute ischemic stroke patients within the 3–4.5 hour time window has been endorsed [42]. Additional exclusion criteria for treating patients in the 3–4.5 hour time window are included in Table 1.6. Ancillary care for patients treated with rtPA between 3 and 4.5 hours is similar to those included in the most recently published guidelines [11]. A final approval decision from the FDA and other regulatory agencies for rtPA in the 3–4.5 hour time window has not been rendered at the time of this writing.

Endovascular stroke treatment

Catheter-based stroke therapies attempt to achieve reperfusion through intra-arterial delivery of thrombolytic agents to the site of thrombotic occlusion, mechanical thromboembolectomy, or a combination of these approaches (Table 1.7). Endovascular approaches to the treatment of acute ischemic stroke are appealing because of relatively low recanalization rates for large artery occlusions [43], risk of drug-induced hemorrhage, and the narrow therapeutic time window associated with intravenous thrombolysis.

Table 1.7. Endovascular interventions for treatment of acute ischemic stroke

Treatment	Comments
Intra-arterial fibrinolysis	Catheter-based treatment of proximal intracranial vascular occlusion. Advantage: direct delivery of fibrinolytic agent to the site of occlusive thrombus; reduced systemic concentration of thrombolytic agent; real-time visualization of occlusion/re-canalization/collateral flow patterns; randomized clinical trial data suggest clinical efficacy of pro-urokinase (PROACT II). Disadvantage: extended "door-to-drug" time; pro-urokinase not available in USA.
Merci Clot Retrieval system	Mechanical helical or "corkscrew" clot-retrieval device deployed distal to occlusion and withdrawn to achieve thrombectomy. Advantage: FDA approved for clot removal up to 8 hours after symptom onset; treatment option for those ineligible for intravenous thrombolytic therapy. Disadvantage: no randomized clinical trial evidence of superior clinical outcomes or functional recovery.
Penumbra system	Mechanical thrombo-aspiration device breaks down clot followed by suction for removal. Advantage: FDA approved for clot removal up to 8 hours after symptom onset; treatment option for those ineligible or refractory to intravenous rtPA. Disadvantage: no randomized clinical trial evidence of superior clinical outcomes or functional recovery.

These advanced stroke therapies are offered in comprehensive stroke centers where personnel experienced in catheter-based stroke treatment and the necessary infrastructure are available.

The clinical efficacy of intra-arterial thrombolysis for treatment of acute ischemic stroke was demonstrated in the Prolyse in Acute Cerebral Thromboembolism II (PROACT II) trial [44]. Patients with angiographically confirmed middle cerebral artery occlusion were randomized to receive either intravenous heparin or 9 mg of intra-arterial pro-urokinase plus intravenous heparin within 6 hours of acute ischemic stroke onset. A recanalization rate of 66% and a statistically significant 15% absolute increase (40% vs. 25%) in favorable outcomes (modified Rankin Score $\leq$ 2) at 90 days was observed in the treatment arm. Symptomatic intracranial hemorrhage was more frequent in the treatment arm (10% vs. 2%), but there was no difference in mortality. Unfortunately, a confirmatory randomized clinical trial necessary for FDA approval was not performed and pro-urokinase is no longer available in the United States. In some centers, the PROACT II results have been extrapolated to justify and guide usage of rtPA for intra-arterial thrombolysis.

Mechanical thrombectomy offers an alternative therapeutic strategy for large clots involving proximal intracranial arteries (i.e. distal carotid terminus or basilar artery) that may be difficult to re-canalize with thrombolytic agents. The Merci Clot Retrieval Device is a flexible wire that assumes a corkscrew shape when deployed distal to the point of occlusion, facilitating entrapment and withdrawal of thromboembolic material. The single-armed, historically controlled MERCI trial demonstrated successful recanalization in 46% of those treated with the helical device within 8 hours of symptom onset [45]. Combined treatment with intravenous rtPA followed by mechanical thrombectomy achieved recanalization in 69% of patients compared to 57% using the device alone [46]. The Penumbra system utilizes a suction catheter to aspirate clot that has been broken down by a separator device. Device approval was based on the results of a prospective, multi-center, single-armed study that achieved an 81.6% re-canalization rate with clinical outcomes and mortality rates comparable to previously published studies [47].

The concept of combined intravenous and intra-arterial fibrinolysis, or so-called "bridging therapy", is attractive because initiation of treatment is not slowed by the inherent delays associated with cerebral angiography. This strategy is being evaluated by The International Management of Stroke (IMS) III trial utilizing an adjusted dose of intravenous rtPA followed by intra-arterial treatment if occlusive thrombus persists on conventional angiography [48]. Patients with moderate to large ischemic strokes (NIHSS $\geq$ 10) are randomized to receive standard