Acute Ischemic Stroke

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Opinion statement

Patients with acute ischemic stroke should be immediately transported to the nearest hospital for rapid evaluation and treatment. Intravenous t-PA within 3 hours of symptom onset is the recommended treatment for patients who meet the National Institute of Neurological Disorders and Stroke (NINDS) study eligibility criteria. Patients should be informed of the risk of symptomatic cerebral hemorrhage, and strict adherence to the NINDS study protocol is strongly recommended to optimize the risk-benefit ratio. Ischemic stroke patients who are not eligible for t-PA therapy should usually be started on aspirin. Intravenous heparin is not recommended as a standard treatment but may be considered for specific patient subgroups. Low-dose subcutaneous heparin is recommended for prophylaxis of deep vein thrombosis in immobilized patients. Management of stroke patients by a designated stroke team is recommended to facilitate prompt diagnosis and treatment and early initiation of rehabilitation therapy. We also recommend that physicians who manage patients with acute stroke maintain contact with local or regional stroke centers to facilitate referral of appropriate patients for intensive care or specialized diagnostic tests or therapies.

Introduction

Stroke is the third leading cause of death (after heart disease and cancer) and the leading cause of serious long-term disability in the United States. Stroke accounts for more than half of all acute neurologic admissions. The vast majority (about 85% in Western societies) of acute strokes have an ischemic basis; the remaining are intracerebral or subarachnoid hemorrhages. Because of the high cost of caring for disabled individuals, even modestly effective treatments for acute stroke are likely to be cost effective. Treatments that are appropriate for a substantial proportion of patients will have the greatest impact on stroke morbidity and mortality. We provide here a brief summary of the available treatment options for acute ischemic stroke and offer our view of the indications for their use in different clinical situations. Readers are also referred to standard guidelines on the subject [1–3].

The publication of the NINDS rt-PA Stroke Study Group trials (NINDS study) has revolutionized treatment of acute ischemic stroke. This group demonstrated that treatment with intravenous t-PA within 3 hours of symptom onset resulted in significant improvement in neurologic outcomes at 3 months [4••, Class I]. Subsequently, acute stroke has been regarded as a medical emergency, and hospital-based systems have been established to facilitate identification, transfer, and diagnosis of stroke victims within 3 hours of onset [5••]. Unfortunately, even under ideal circumstances, only a minority of all patients with acute stroke arrive at a hospital in time to receive t-PA.

For patients treated with intravenous t-PA within 6 hours of stroke onset, neither the two European Cooperative Acute Stroke Studies (ECASS I and II) nor the North American Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) trial documented significant benefits from thrombolytic therapy [6•,7•,8, Class I]. In addition, in ECASS I, t-PA treatment appeared to increase substantially the risk of fatal cerebral hemorrhage in patients with major early infarct signs involving more than one third of the middle cerebral artery (MCA) territory on the baseline CT scan [6•,9, Class II]. Although these signs can be subtle and difficult to identify reliably, at present the ECASS CT exclusion criteria are often employed as an adjunct to the NINDS study exclusion criteria for treatment of patients with ischemic stroke within the 3-hour time

window. Whether it is appropriate to apply these criteria to the 3-hour time window is not clear.

For patients who are not treated with intravenous t-PA and are not receiving intravenous anticoagulation or oral warfarin, early aspirin therapy should be commenced if not contraindicated. Oral administration of aspirin within 48 hours of symptom onset was recently shown to provide a small benefit in both short- and long-term outcome in the International Stroke Trial (IST) and the Chinese Acute Stroke Trial (CAST) [10•,11•, Class I].

Anticoagulation with heparin is commonly used in acute ischemic stroke, especially for patients with progressing or cardioembolic stroke. There are conflicting data regarding the safety and efficacy of heparin, however. In the IST, use of subcutaneous heparin was associated with fewer early recurrent ischemic strokes, but increases in the incidence of brain hemorrhage and extracranial bleeding offset this benefit. The occurrence of hemorrhagic strokes and early deaths substantially increased with the use of high-dose (12,500 U bid) subcutaneous heparin. Bleeding rates in the low-dose (5000 U bid) subcutaneous heparin groups were similar to those associated with aspirin therapy alone. The combined use of low-dose subcutaneous heparin and aspirin was safe in the IST and was associated with the lowest rate of early stroke recurrence and pulmonary embolism but did not appear to improve long-term outcome more than aspirin alone [10•, Class I]. Similarly, in the recently published Trial of ORG 10172 in Acute Stroke Treatment (TOAST) study, the use of intravenous danaparoid (a low-molecular-weight heparinoid substance) did not alter neurologic outcome at 3 months compared with placebo [12•, Class I]. Therefore, anticoagulation should not be used routinely in acute ischemic stroke.

NEUROIMAGING

The use of intravenous t-PA within a 3-hour time window as a standard treatment for all eligible patients with ischemic stroke is not uniformly endorsed by stroke neurologists and emergency medicine specialists [13,14]. It has been proposed that the use of intravenous t-PA in some patient subgroups may not be beneficial and could expose these patients to the unnecessary risks of intracranial and systemic hemorrhage. These subgroups might include 1) patients in whom arterial occlusion has undergone spontaneous recanalization; 2) patients in whom arterial occlusion is unlikely to recanalize with intravenous t-PA (*eg*, internal carotid artery occlusions or occlusions of small deep penetrating arteries); and 3) patients whose neurologic deficits are not due to stroke (*eg*, migraine aura, postictal paresis, and functional deficits).

The recent preliminary reports of negative results in two large trials of intravenous t-PA administered within 6 hours of symptom onset (ECASS II and ATLANTIS) indicate that intravenous t-PA at a dose of 0.9 mg/kg is not significantly beneficial for patients selected on the basis of the NINDS study eligibility criteria beyond a 3-hour window [7•,8, Class I]. These findings suggest the need for a more specific definition of the underlying pathophysiology to assist in selecting the most appropriate therapy in individual patients. Modern neuroimaging techniques may provide useful data to allow extension of the therapeutic time window for intravenous t-PA beyond 3 hours in selected patients. These techniques might also facilitate patient selection for intra-arterial thrombolysis.

Using CT, magnetic resonance imaging (MRI), and ultrasound techniques, it is now possible to obtain information regarding the size and location of the acute ischemic lesion, tissue characteristics of the early infarct, the site of arterial occlusion, the presence of collateral circulation, and the status of cerebral perfusion within a relatively short period of time (Table 1).

Identification of signs of early infarct is difficult on CT in the acute stage, especially in the posterior fossa. Diffusion-weighted imaging (DWI) MRI provides a highly reliable anatomic localization of nearly all acute infarcts and is highly sensitive and specific for distinguishing between acute and chronic infarcts [15•]. A gradient echo sequence can be included in an MRI-based acute stroke protocol to help exclude the presence of cerebral hemorrhage [16•]. The sensitivity and specificity of MRI for detection of ultra-acute brain hemorrhage, however, have not been clearly defined. In addition, early signs of infarct on MRI as a predictor of thrombolytic response have not yet been studied in clinical trials.

Trancranial Doppler (TCD) can provide information about blood flow in the circle of Willis and its proximal branches but is at times limited by absence of acoustic bone windows, especially in elderly patients [17]. CT and magnetic resonance angiography can provide good delineation of the entire extracranial and intracranial vasculature. CT angiography, in addition, can provide information regarding the status of leptomeningeal collaterals. The presence of good collateral blood flow may predict a good response to thrombolysis [18]. Perfusion studies, including single photon emission computed tomography (SPECT), xenon CT, and perfusion-weighted MRI imaging (PWI), could allow exclusion of patients from thrombolytic therapy who demonstrate normal cerebral blood flow, which may be due to spontaneous early reperfusion [19]. In addition, these imaging studies can potentially identify a subgroup of patients who either have a high risk of hemorrhagic transformation following thrombolysis [20] or have an increased likelihood of developing life-threatening cerebral edema and herniation [21] because of severe widespread hypoperfusion. Use of subtraction imaging with CT angiography can also

Table 1. Neuroradiologic assessment of acute ischemic stroke

Approach	Lesion size/location	Vascular occlusion	Cerebral perfusion	Advantages	Disadvantages
CT based	Head CT—early infarct signs	CT angiography	Xenon CT	Good availability* Minimal time required* Gold standard for excluding ICH	Early infarct signs are often very subtle Xenon CT requires patient cooperation
MRI based	Diffusion-weighted images	MR angiography	Perfusion-weighted images	Most accurate identification of size and location of early infarct Perfusion/diffusion mismatch may predict infarct progression	Limited availability at present Requires more patient cooperation than CT (motion artifacts)
Mixed	Head CT—early infarct signs	Transcranial Doppler Carotid ultrasound	SPECT	Requires minimal patient cooperation Widely available†	Requires substantially more time than single modality approaches Accuracy of ultrasound techniques highly operator dependent

*Availability is limited for xenon CT, and the time required may be significantly increased.
†Except for SPECT imaging.
ICH—intracranial hemorrhage; MR—magnetic resonance; MRI—magnetic resonance imaging; SPECT—single photon emission computed tomography.

provide an estimate of cerebral blood flow [22]. This technique could potentially be used in place of xenon CT and thereby reduce the time required for a CT-based approach to acute stroke evaluation.

Recently, there has also been interest in the subgroup of patients who present with "diffusion-perfusion mismatch." In these patients, the lesion seen on DWI is smaller than the lesion seen on PWI during the early stage of stroke. These patients typically demonstrate subsequent expansion of the lesion on DWI, and the ultimate site of the DWI lesion corresponds closely with the final volume of brain infarction [23,24]. This expansion may be preventable with thrombolytic or neuroprotective therapy. Therefore, DWI-PWI mismatch might be helpful for selecting subgroups of patients that are most likely to benefit from acute therapies.

Treatment

General medical treatment

- Organized inpatient care for stroke patients in "stroke units" has been shown to reduce long-term mortality, disability, and institutionalization [25•, Class I]. Therefore, hospitalized stroke patients should be managed by a team with special interest in stroke. This approach facilitates rapid evaluation, monitoring, and management. Hospital-based stroke programs typically provide organized nursing and rehabilitative care, early planning for discharge and long-term therapy, and education of patients and relatives.
- The stroke team approach also facilitates development of acute treatment protocols, enrollment of patients in clinical trials, and interactions between specialists in neurology, neurosurgery, neuroradiology, emergency medicine, critical care medicine and rehabilitation medicine. These interactions foster a multidisciplinary approach to stroke treatment.
- Hypertension is common after acute ischemic stroke. There are limited data available to address the optimal management of blood pressure following stroke. Because of the potential risk of causing extension of the infarct, we do

not usually treat hypertension during the first few days after stroke onset unless it is associated with hypertensive encephalopathy or medical conditions such as pulmonary edema, congestive heart failure, myocardial ischemia, and aortic dissection. We cautiously reduce elevated blood pressure in patients who suffer from hemorrhagic conversion of infarct with significant hematoma formation. For patients with pre-existing hypertension, we typically reduce the dose of their regular antihypertensive medication or withhold antihypertensive treatment if the blood pressure is not grossly elevated during the immediate poststroke period. In patients who receive thrombolytic treatment, blood pressure level should be maintained below 180/105 mm Hg (following the NINDS study protocol) for 24 to 36 hours after treatment to minimize the risk of symptomatic cerebral hemorrhage.

- Hyperthermia within 6 hours of acute stroke is associated with increased mortality [26, Class II], and experimental animal studies indicate that hyperthermia exacerbates ischemic neuronal injury. We recommend that stroke patients with body temperature of more than 38°C be actively treated with antipyretics, fully investigated for possible sources of infection, and started on early antibiotic therapy.
- Hyperglycemia in diabetic patients with stroke often requires sliding-scale insulin coverage in addition to regular treatment. Hyperglycemia in nondiabetic stroke patients may be due to the stress response but also appears to be associated with a worsened prognosis [27, Class II]. There are no data to address whether early treatment is beneficial, but we recommend maintenance of reasonable glycemic control in all acute stroke patients.
- Steroid treatment in acute ischemic stroke is of no significant benefit [28, Class I] except when vasculitis is the underlying cause.
- Most stroke patients should have an assessment of swallowing on admission with a screening timed water-swallow test at the bedside and, if necessary, assessment by a speech therapist. Patients who fail the swallowing assessment should have a nasogastric tube inserted by the second day after hospital admission to allow feeding. If it appears unlikely that the patient will be able to resume oral feeding within a few weeks, early placement of a percutaneous gastric or duodenal feeding tube is recommended [29, Class II].

Intensive care treatment

- Specific subgroups of patients with acute ischemic stroke require admission to an intensive care unit. These include patients who receive 1) mechanical ventilation, 2) monitoring and treatment of significantly elevated intracranial pressure (ICP), or 3) inotropic support with aggressive fluid and blood pressure management. In addition, patients who receive thrombolytic therapy are usually admitted to either an intensive care unit or a specialized ward where facilities and trained staff are available for continuous electrocardiographic monitoring and frequent checks of blood pressure and neurologic status for at least 24 hours after treatment.
- Mechanical ventilation is most often required for patients with acute stroke with impaired ventilatory drive due to compromised brain stem respiratory centers. This may occur acutely in patients with severe brain stem infarcts but usually occurs during the second to fifth day after symptom onset in patients suffering from large hemispheric infarctions complicated by massive cerebral edema or hematoma formation, which results in transtentorial herniation. Impaired respiration may also occur after a similar time course because of brain stem compression secondary to large edematous cerebellar

infarcts. Mechanical ventilation is sometimes also required for patients with impaired airway protection or when sedation is necessary to perform procedures (*eg*, angiography).

- Frequent neurologic observation is required for patients with acute stroke with significantly increased ICP. Signs of impending herniation include dilatation and decreased reactivity of the pupil ipsilateral to the infarct and an increase in mean arterial blood pressure associated with bradycardia. In unconscious patients, motor response to painful stimuli should also be monitored. Intracranial pressure monitoring devices, such as intraventricular catheters or subarachnoid bolts, may be helpful in guiding therapy.
- Medical management of increased ICP involves osmotherapy and hyperventilation. Surgical decompression may be considered in situations in which maximal medical treatment is unlikely to be effective but satisfactory outcomes are still possible after surgery [30,31•, both Class III]. Head elevation to 30° and treatment of hypoxia, hypercapnia, fever, and seizures are simple measures that can reduce ICP. Sedatives or muscle relaxants may also be used to reduce increases in ICP caused by agitation during mechanical ventilation.
- Mannitol is the most commonly used agent in osmotherapy. It is usually given at a dose of 0.5 to 2.0 g/kg intravenously over 30 minutes, which can be repeated every 4 to 6 hours. A rebound increase in ICP may occur, possibly owing to accumulation of the agent in ischemic brain tissue. The main side effects of mannitol are hypotension, hypokalemia, hemolysis, and congestive heart failure. It is probably not effective when the plasma osmolality is more than 315 to 320 mOsm/kg. Levels of serum electrolytes, urea, and creatinine and serum and urine osmolalities should be closely monitored. Glycerol and hypertonic saline are alternative osmotic agents that are less commonly used.
- Hyperventilation, with a target $PaCO_2$ of 25 to 30 mm Hg, provides short-term reductions in ICP. This effect is mediated by cerebral vasoconstriction. Excessive hyperventilation ($PaCO_2$ of less than 25 mm Hg) may result in worsening cerebral ischemia because of excessive vasoconstriction. Placement of a catheter in the internal jugular vein bulb allows monitoring of venous oxygen saturation. A low reading (less than 50%) suggests excessive cerebral oxygen extraction and implies that hyperventilation and hypocapnia may be excessive. Other treatments, such as more intensive osmotherapy and correction of underlying medical conditions (including anemia and systemic hypotension), may also improve oxygen delivery to the brain.
- Patients with acute stroke who are also suffering from myocardial ischemia, congestive heart failure, pulmonary edema, hypovolemia, or renal failure typically require close monitoring in an intensive care unit. The goals of therapy are to optimize fluid status, blood pressure, and cardiac output to maintain adequate cerebral perfusion pressures and avoid extension of the cerebral infarct. Placement of a central venous catheter and, occasionally, a Swan-Ganz catheter may be needed for monitoring of central venous pressure and the pulmonary capillary wedge pressure. In addition, a subset of patients with acute ischemic stroke, particularly those with multifocal large-artery cerebrovascular occlusive disease, experience neurologic improvement with pharmacologic elevation of blood pressure above a threshold value [32, Class III]. Therapeutic options for these patients include intravenous volume expansion with colloids or crystalloids. Inotropic support with agents like dopamine, dobutamine, or phenylephrine may also be considered for selected hypotensive patients.

- Despite maximal medical treatment, complete MCA territory infarction carries a high mortality rate owing to transtentorial herniation [33•]. For brain stem infarctions due to basilar artery thrombosis, intraarterial thrombolysis has been successful for some patients. This condition is still associated with a high mortality, however, and many survivors are either ventilator dependent or in a vegetative or locked-in state. It is appropriate to have early discussions with high-risk patients and their relatives regarding the prognosis and the possible use of cardiopulmonary resuscitation and mechanical ventilation. "Do-not-resuscitate" orders may be appropriate for some high-risk patients depending on the wishes of the patient and family members [34].

Pharmacologic treatment

- Intravenous t-PA should be considered for all patients with acute ischemic stroke who meet the inclusion and exclusion criteria used in the NINDS trial and who can be treated within 3 hours of stroke onset [4••, Class I]. The NINDS study protocol should be strictly followed, because when this is done, postmarketing experience with this agent in both teaching and community hospitals has reproduced the favorable outcomes documented in patients treated with t-PA in the NINDS study [35,36]. Protocol violation was associated with less favorable outcomes.
- The use of intravenous streptokinase within 4 to 6 hours of stroke onset is associated with a high incidence of cerebral hemorrhage and early mortality [37–39, Class I] and is not recommended.
- Anticoagulation with intravenous heparin cannot be recommended for routine clinical use in the setting of acute ischemic stroke [10•,12•, Class I]. Careful use of intravenous heparin with dose titration to maintain a partial thromboplastin time (PTT) 1.5 to 2.0 times the control value remains a reasonable therapeutic option in certain patient groups, however. The availability of low-molecular-weight heparin, which can be administered by twice-daily subcutaneous injection without the need for frequent blood draws to monitor coagulation profiles, may allow early discharge of anticoagulated patients and can result in significant cost savings on hospitalization.
- Low-dose subcutaneous heparin is recommended in immobile stroke patients for prophylaxis of deep vein thrombosis and pulmonary embolism.
- For patients with acute ischemic stroke who are not treated with thrombolytic therapy and are not receiving intravenous or oral anticoagulation, early aspirin therapy should be commenced within 48 hours of symptom onset [10•,11•, Class I].

Intravenous tissue plasminogen activator

Intravenous tissue plasminogen activator (t-PA, alteplase) is indicated in patients 18 years of age or older with a clinical diagnosis of ischemic stroke presenting with a measurable neurologic deficit in whom the time of symptom onset is well established to be within 180 minutes of beginning t-PA treatment. Clinical discretion and judgment are necessary, because the use of intravenous t-PA may be associated with a decreased chance of benefit or an increased possibility of cerebral hemorrhage in some patient subgroups, including patients older than 85 years of age, those with a severe stroke (NIH Stroke Scale score of greater than 22), those with brain edema or mass effect, or those with signs of early infarct involving more than one third of the MCA territory on the initial noncontrast CT brain scan. We use intravenous t-PA in selected patients in these subgroups

because benefits of treatment appeared to occur in the NINDS study in these patients [40]. We caution the patient and family members about the increased risk of symptomatic cerebral hemorrhage, however. We withhold t-PA in patients presenting with rapidly improving neurologic deficit or minor deficits with an NIH Stroke Scale score of less than 3 or 4 because they usually have excellent recovery without therapy.

Standard dosage 0.9 mg/kg (maximum dose 90 mg), with 10% of the total dose administered as an initial intravenous bolus over 1 minute and the remaining dose infused over 60 minutes.

Contraindications Evidence of intracranial hemorrhage on pretreatment CT scan; clinical presentation suggestive of subarachnoid hemorrhage (sudden severe headache, neck stiffness, and altered mental status), even with normal CT; active internal bleeding; known bleeding diathesis, including platelet count of less than 100,000/mm^3, use of heparin within 48 hours with a PTT greater than the upper normal limits, or current or recent oral anticoagulant therapy with a prothrombin time of more than 15 seconds; intracranial surgery, serious head trauma, or previous stroke occurring less than 3 months previously; known intracranial arteriovenous malformation or aneurysm; major surgery or serious trauma (exclusive of head trauma) within the previous 14 days; history of gastrointestinal or urinary tract hemorrhage within 21 days; recent myocardial infarction; recent arterial puncture at a noncompressible site; recent lumbar puncture; abnormal blood glucose (less than 50 or more than 400 mg/dL); systolic blood pressure of more than 185 mm Hg or diastolic blood pressure of more than 110 mm Hg on repeated measurements at the time treatment is to begin (or if the patient requires aggressive measures to reduce blood pressure to within these limits); or seizure at the time of onset of stroke symptoms.

Main drug interactions Heparin, warfarin, aspirin, or any other antithrombotic therapy should not be used during the first 24 hours after t-PA administration to minimize the risk of intracranial or systemic hemorrhage.

Main side effects In the NINDS study, within 36 hours of the initiation of t-PA treatment, intracerebral hemorrhage occurred in 10.6% of patients. Hemorrhage associated with neurologic deterioration occurred in 6.4%, and 2.9% had a fatal hemorrhage (*ie*, nearly 50% of the symptomatic hemorrhages were fatal). Special care should also be taken to monitor for systemic hemorrhage in critical or occult locations (gastrointestinal, retroperitoneal, urinary, or pericardial). Anaphylactic reactions, which present with hypotension, urticaria, or angioedema, may rarely occur.

Special points Tissue plasminogen activator should be administered only in hospitals fulfilling the following requirements. 1) Neurologic or emergency department expertise should be available for prompt clinical evaluation of the patient and interpretation of the initial CT brain scan, and expert radiologic opinion should be available if needed for CT interpretation. 2) Facilities such as a stroke unit or an intensive care unit should be available for close monitoring of the patient's vital signs and neurologic status for at least the first 24 hours after treatment. The aim is to maintain a blood pressure below 180/105 mm Hg, with the use of antihypertensive medications if necessary. 3) A management plan should be available for possible intracranial hemorrhage. Symptoms suggestive of symptomatic intracranial hemorrhage include neurologic deterioration, headache, acute hypertension, nausea, and vomiting. Initial treatment consists of discontinuation of the t-PA infusion if suspicious symptoms occur and obtaining a head CT scan. Reversal of coagulation abnormalities with transfusions of cryoprecipitate, fresh frozen plasma, and platelets should be considered and a neurosurgical opinion obtained if CT confirms the diagnosis.

Cost effectiveness In the NINDS study, the average length of hospital stay was significantly shorter in patients treated with t-PA than in patients who received placebo, and more treated patients were discharged home than to inpatient rehabilitation units or nursing homes. It is highly likely that the additional hospitalization costs incurred with the use of t-PA are recovered within a year compared with the cost of long-term care [41].

Aspirin

	Patients with acute ischemic stroke presenting within 48 hours of symptom onset who are not being treated with thrombolytic agents, anticoagulants, or other antiplatelet medications should usually be administered aspirin. Aspirin is also effective as a long-term treatment for secondary prophylaxis of ischemic stroke after transient ischemic attack or ischemic stroke.
Standard dosage	160 to 325 mg orally as an initial dose and 81 to 325 mg daily as a maintenance dose. The higher initial dose is necessary to achieve early inhibitory effect on platelet aggregation. An 81-mg tablet or an enteric-coated preparation may be used for long-term maintenance to decrease the gastrointestinal side effects.
Contraindications	Evidence of significant intracranial hemorrhage on CT brain scan or clinical suspicion of its presence; active gastrointestinal or systemic bleeding; known bleeding diathesis; or use of thrombolytic agent within the past 24 hours.
Main drug interactions	Monitor closely when used concomitantly with anticoagulants, other drugs irritating to the gastrointestinal tract, other ototoxic drugs, lithium carbonate, probenecid, and other drugs that are highly protein bound.
Main side effects	Intracranial hemorrhage, systemic (mainly gastrointestinal) bleeding, gastrointestinal upset, bronchospasm, and tinnitus.
Special points	The use of aspirin in combination with warfarin or heparin increases the risks of intracranial and systemic hemorrhage and is usually not recommended. The combined use of aspirin and low-dose subcutaneous heparin appears safe in patients with acute stroke, however.
Cost effectiveness	Although early aspirin use in unselected patients with acute ischemic stroke is associated with only small absolute benefits (about 1%) in early or late morbidity and mortality, the low cost of aspirin and its wide application enables this treatment to be cost effective.

Heparin

	Early administration of intravenous heparin to achieve anticoagulation may be considered in selected patient groups with acute ischemic stroke. These include 1) patients with progressing or fluctuating neurologic deficits with extracranial or intracranial large-vessel atherothrombotic disease believed to be the cause of the stroke and 2) patients with cardiac conditions that are believed to be the cause of stroke and that place the patient at a significantly increased risk of early recurrence of stroke. These cardiac conditions include atrial fibrillation, mechanical valvular prosthesis, dilated cardiomyopathy with gross impairment of left ventricular function, and acute anterior myocardial infarction, particularly with the presence of a left ventricular thrombus. Anecdotal experience also suggests that early anticoagulation may be useful in the following patients. 1) Those with a documented severe symptomatic carotid stenosis (90% to 99%) when carotid endarterectomy is deferred because of the occurrence of acute stroke. Anticoagulation is often used in the hope of decreasing the risks of vessel occlusion and thromboembolic complications while awaiting surgery. 2) Patients with carotid or vertebral dissection, because anticoagulation may decrease the risk of thromboembolism. 3) Patients with ischemic stroke secondary to cerebral venous sinus thrombosis. The use of anticoagulation was associated with improved clinical outcome in some case series and one small randomized trial [42, Class II]. 4) Patients with congenital or acquired hypercoagulable conditions (*eg*, antiphospholipid antibody syndrome and protein C, protein S, or antithrombin III deficiencies) that are believed to be the cause of their strokes. Low-dose subcutaneous heparin is indicated in virtually all immobile stroke patients for prophylaxis of deep venous thrombosis and pulmonary embolism.
Standard dosage	Starting dose is usually 800 to 1000 units/h given as a continuous intravenous infusion. An initial bolus dose is usually omitted for stroke patients in the hope of minimizing the risk of cerebral hemorrhage. PTT is checked 4 to 6 hours after dose initiation, at every change of dose, and at least daily while on a stable dose. The dose of heparin is titrated to maintain a PTT of 1.5 to 2.0 times the control value. Low-dose heparin is usually administered subcutaneously at a dose of 5000 IU bid.

Contraindications Intracranial hemorrhage or significant hemorrhagic conversion of the cerebral infarct (a CT head scan is required before starting heparin in stroke patients); lumbar puncture or the presence of an indwelling epidural catheter; infective endocarditis; bleeding diathesis; thrombocytopenia; hepatic failure; active gastrointestinal bleeding; uncontrolled severe hypertension; recent trauma or surgery to the head, spine, or orbit; and history of heparin-induced thrombocytopenia or thrombosis. In addition, according to the NINDS study criteria, heparin should be withheld for at least 24 hours after the use of intravenous t-PA in patients with acute stroke.

Main drug interactions Concomitant use of aspirin or other platelet inhibitors increases the risk of bleeding; therefore, antiplatelet therapy is usually not given in combination with intravenous heparin to patients with stroke, except under special circumstances.

Main side effects Hemorrhage, thrombocytopenia, "white clot" syndrome, local injection site reaction, hypersensitivity, and osteoporosis.

Special points Monitor platelet count, hematocrit, and fecal occult blood while the patient is receiving heparin. Heparin should be discontinued immediately if significant intracranial or systemic hemorrhage is suspected, platelet count is less than 100,000/mL, or recurrent thrombosis occurs. Protamine sulfate, 1 mg, given by slow intravenous injection neutralizes 90 units of bovine heparin or 115 units of porcine heparin.

Cost effectiveness Because reliable data confirming the beneficial effects of heparin use in patients with acute stroke are not available, it is difficult to determine whether heparin therapy is cost effective. We frequently discharge clinically stable and nondisabled patients who are treated with anticoagulation therapy and give them a 5-day course of low-molecular-weight heparin injections (*eg*, enoxaparin, 1 mg/kg bid subcutaneously) while awaiting their prothrombin times to become therapeutic with use of oral warfarin. This makes early discharge possible in many anticoagulated stroke patients and results in significant savings in hospitalization charges.

Interventional procedures

- Intra-arterial administration of thrombolytic agents requires the expertise of a neurointerventional specialist and is offered in a limited number of centers to highly selected patients with acute ischemic stroke. In comparison with intravenous thrombolysis, this technique has the advantage of definite localization of the site of arterial occlusion. In some series, higher rates of arterial recanalization in carotid territory strokes and improved outcome compared with historical controls in patients with basilar artery thrombosis were demonstrated [43,44, both Class III]. One randomized phase III clinical trial limited to patients with an acute middle cerebral artery occlusion has been completed recently, with preliminary results indicating that there was a beneficial effect if treatment was begun within 6 hours of symptom onset [45]. While awaiting the full report of this trial and further evidence of its therapeutic efficacy in ischemic strokes involving other vascular territories, intra-arterial thrombolysis should be considered an investigational treatment.
- Percutaneous transluminal angioplasty has been used as an adjunct to intra-arterial thrombolysis in patients who developed rethrombosis after successful thrombolytic treatment and in individuals considered to be at high risk of developing reocclusion because of significant focal residual arterial stenosis [46, Class III]. More recently, a few centers have begun to use direct angioplasty in selected patients with acute stroke who present with initial CT findings of significant signs of early infarct, which may be associated with an increased risk of developing symptomatic cerebral hemorrhage following thrombolytic therapy [47, Class III]. Clinical experience with this technique in acute stroke patients is very limited, however.

Surgery

- Decompressive craniectomy is indicated for treatment of large cerebellar infarcts in patients with clinical deterioration and evidence of early brain stem compression or hydrocephalus [30, Class III]. More recently, hemicraniectomy has been performed in selected patients with complete middle cerebral artery territory infarction who are at significant risk of developing transtentorial herniation; favorable outcomes are reported in some case series [31•, Class III]. We consider early surgical decompression as a treatment option for suitable patients with either large cerebellar or hemispheric infarctions.
- Carotid endarterectomy for significant symptomatic internal carotid artery stenosis is typically deferred 4 to 6 weeks in patients with an acute stroke because the risks of perioperative stroke and hemorrhagic conversion of the infarct appear to be increased during the immediate poststroke period. Recent data from the North American Symptomatic Carotid Endarterectomy Trial demonstrated that early endarterectomy (within 30 days of stroke onset) can be performed safely in patients with minor nondisabling strokes [48, Class II]. Early surgery should be considered in patients with very severe stenosis who have small infarcts. Patients who develop acute carotid thrombosis after endarterectomy should be considered for urgent surgical reexploration and thrombectomy.

Emerging therapy

- Other promising antithrombotic agents that are currently being evaluated in acute ischemic stroke include the following. 1) Ancrod, a snake venom extract that possesses a fibrinogen-depleting effect. A phase III clinical trial has been completed, and preliminary results showed beneficial effects if this agent was started within 3 hours of stroke onset [49]. 2) Glycoprotein IIb/IIIa antagonists. These agents block the final common pathway involved in platelet aggregation. Abciximab, an agent of this class of compounds, is currently undergoing a phase II clinical trial.
- Sequential use of intravenous and intra-arterial thrombolysis carries theoretical advantages. Thrombolysis can be initiated rapidly by the intravenous route (and possibly at a lower initial dose) when a patient presents to a community hospital and is assessed within 3 hours of symptom onset. Subsequently, the patient may be transferred immediately to a regional stroke center for consideration of additional intra-arterial thrombolytic therapy if the occluded vessel has not been recanalized.
- A cascade of biochemical reactions is involved in acute ischemic stroke, culminating in neuronal injury. These reactions include activation of glutamate receptors, influx of calcium ions into neurons, formation of nitric oxide, generation of free radicals and lipid peroxidation, secondary inflammatory reactions due to leukocyte migration, and reperfusion injury. Many pharmacologic agents produce a substantial neuroprotective effect in animal models of acute ischemic stroke, and several of these have been evaluated in human clinical trials. Unfortunately, none of these agents has proven to be effective in humans. Possible explanations for the discrepancies between the results in animal studies and in human trials include the following. 1) Neuroprotective agents are typically effective in animal models only when administered within 2 hours of stroke onset. In human trials, these agents have usually been administered between 4 and 6 hours of symptom onset or even later. 2) Animal models of stroke typically show neuroprotective effects for large cortical or subcortical lesions, whereas clin-

ical trials have enrolled a wide variety of stroke subtypes (*eg*, lacunar strokes, brain stem lesions). 3) Animal models of stroke may have better collateral circulation for delivery of the neuroprotective agent to the ischemic area. 4) Dose-limiting side effects of an agent in humans may result in subtherapeutic drug levels (*eg*, neurobehavioral side effects of NMDA [N-methyl-D-aspartate] agonists), and adverse effects may counteract potential therapeutic benefits (*eg*, hypotensive effect of calcium channel blockers). 5) Application of a biological agent that is effective in animals may be inappropriate in human subjects (*eg*, the use of a murine monoclonal antibody against human intracellular adhesion molecule-I was associated with worsened neurologic outcome and an increased rate of fever and infections in human stroke patients).

- Combination therapy with neuroprotective and thrombolytic agents has been assessed in some recent phase II trials. Rationales for this approach include 1) improved delivery of neuroprotective agents to the ischemic area with successful arterial recanalization, 2) reduction of reperfusion injury potentially associated with thrombolytic therapy by neuroprotective agents, and 3) possible synergistic effect with the combined use of thrombolysis and neuroprotection.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of special interest
- •• Of outstanding interest

1. Adams HP, Brott TG, Crowell RM, *et al.*: **Guidelines for the management of patients with acute ischemic stroke: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association.** *Stroke* 1994, **25:**1901–1914.
2. Adams HP, Brott TG, Furlan AJ, *et al.*: **Guidelines for thrombolytic therapy for acute stroke: a supplement to the guidelines for the management of patients with acute ischemic stroke. A statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association.** *Stroke* 1996, **27:**1711–1718.
3. Albers GW, Easton JD, Sacco RL, Teal P: **Antithrombotic and thrombolytic therapy for ischemic stroke.** *Chest* 1998, **114:**683S–698S.
4. •• The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group: **Tissue plasminogen activator for acute ischemic stroke.** *N Engl J Med* 1995, **333:**1581–1587.

In this trial, patients treated with intravenous t-PA at a dose of 0.9 mg/kg begun within 3 hours of symptom onset were at least 30% more likely to have a favorable outcome (absolute benefit 11% to 13%) after 3 months when compared with patients given placebo. In addition, there was no increase in the number of early or late deaths or in late disability attributable to t-PA. Since these favorable results were not replicated by the ECASS trials and the streptokinase trials, the protocol and the inclusion and exclusion criteria of this study should be followed closely when intravenous t-PA is administered to patients with stroke.

5. •• The National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study Group: **A systems approach to immediate evaluation and management of hyperacute stroke: experience at eight centers and implications for community practice and patient care.** *Stroke* 1997, **28:**1530–1540.

This paper describes specific measures to minimize the amount of time between stroke onset and treatment. These measures include community education and coordination among emergency medical services and stroke teams. Standard orders, patient selection criteria for intravenous t-PA therapy, and algorithms for management of elevated blood pressure and suspected intracranial hemorrhage are provided.

6. • Hacke W, Kaste M, Fieschi C, *et al.*: **Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke: the European Cooperative Acute Stroke Study (ECASS).** *JAMA* 1995, **274:**1017–1025.

This trial demonstrated that intravenous t-PA in a dose of 1.1 mg/kg given to patients with hemispheric stroke within 6 hours of symptom onset was associated with increased cerebral hemorrhage and early death, especially in patients with CT signs of early infarction involving more than 33% of the MCA territory.

7.• Hacke W, Kaste M, Fieschi C, *et al.*: **Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II).** *Lancet* 1998, **352:**1245–1251.

In this recently published study, intravenous t-PA in a dose of 0.9 mg/kg was given within 6 hours of stroke onset using a protocol similar to that of the NINDS study. No significant benefits or risks were detected in this trial. In addition, preliminary reports suggest that CT signs of early infarction did not seem to predict the clinical response to intravenous t-PA in this study.

8. Clark WM, Albers GW, for the ATLANTIS Stroke Study Investigators: **The ATLANTIS rt-PA (alteplase) acute stroke trial: final results.** *Stroke* 1999, **30:**234.

9. von Kummer R, Allen KL, Holle R, *et al.*: **Acute stroke: usefulness of early CT findings before thrombolytic therapy.** *Radiology* 1997, **205:**327–333.

10.• International Stroke Trial Collaborative Group: **The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19,435 patients with acute ischaemic stroke.** *Lancet* 1997, **349:**1569–1581.

In this study, the use of subcutaneous heparin was not found to reduce significantly the risk of early stroke recurrence. Even in the subgroup with atrial fibrillation, the reduction in recurrence of ischemic stroke with subcutaneous heparin (2.8% versus 4.9%) was largely counterbalanced by an increase in hemorrhagic stroke (2.1% versus 0.4%), rendering the net benefit not significant.

11.• CAST (Chinese Acute Stroke Trial) Collaborative Group: **CAST: randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke.** *Lancet* 1997, **349:**1641–1649.

Aspirin started within 48 hours of ischemic stroke onset at a dose of 160 to 300 mg daily resulted in nine fewer deaths or nonfatal strokes during the first 2 to 4 weeks and 13 fewer deaths or cases of dependency in 4 weeks to 6 months after stroke onset per 1000 patients treated.

12.• The Publications Committee for the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Investigators: **Low molecular weight heparinoid, ORG 10172 (danaparoid), and outcome after acute ischemic stroke: a randomized controlled trial.** *JAMA* 1998, **279:**1265–1272.

This study classified the causes of stroke into the subgroups of large artery atherosclerosis, cardioembolism, small vessel disease, and uncertain cause. Although no overall benefit at 3 months was demonstrated with the use of intravenous danaparoid, on subgroup analysis there were significantly more patients with large artery atherosclerosis who had a favorable outcome at 3 months in the group treated with danaparoid.

13. Caplan LR, Mohr JP, Kistler JP: **Thrombolysis—not a panacea for ischemic stroke.** *N Engl J Med* 1997, **337:**1309–1310.

14. Wardlaw JM, Warlow CP, Counsell C: **Systematic review of evidence on thrombolytic therapy for acute ischaemic stroke.** *Lancet* 1997, **350:**607–614.

15.• Lutsep HL, Albers GW, DeCrespigny A, *et al.*: **Clinical utility of diffusion-weighted magnetic resonance imaging in the assessment of ischemic stroke.** *Ann Neurol* 1997, **41:**574–580.

Diffusion-weighted imaging is especially useful in early detection and localization of brain infarction within 48 hours of stroke onset, particularly for small subcortical and brain stem infarcts. It also allows one to distinguish between acute and chronic infarcts.

16.• Patel MR, Edelman RR, Warach S: **Detection of hyperacute primary intraparenchymal hemorrhage by magnetic resonance imaging.** *Stroke* 1996, **27:**2321–2324.

In this study, magnetic resonance susceptibility-weighted gradient-echo images and echo-planar imaging T2-weighted images were able to demonstrate acute cerebral hemorrhage with a core of signal loss and a rim of surrounding hyperintensity. Other magnetic resonance techniques are also being evaluated to detect subarachnoid or intraventricular hemorrhages. These techniques may render the CT scan unnecessary for the exclusion of intracranial bleeding in the evaluation of acute stroke.

17. Alexandrov AV, Bladin CF, Norris JW: **Intracranial blood flow velocities in acute ischemic stroke.** *Stroke* 1994, **25:**1378–1383.

18. Wildermuth S, Knauth M, Brandt T, *et al.*: **Role of CT angiography in patient selection for thrombolytic therapy in acute hemispheric stroke.** *Stroke* 1998, **29:**935–938.

19. Firlik AD, Rubin G, Yonas H, Wechsler LR: **Relation between cerebral blood flow and neurologic deficit resolution in acute ischemic stroke.** *Neurology* 1998, **51:**177–182.

20. Ueda T, Hatakeyama T, Kumon Y, *et al.*: **Evaluation of risk of hemorrhagic transformation in local intra-arterial thrombolysis in acute ischemic stroke by initial SPECT.** *Stroke* 1994, **25:**298–303.

21. Firlik AD, Yonas H, Kaufmann A, *et al.*: **Relationship between cerebral blood flow and the development of swelling and life-threatening herniation in acute ischemic stroke.** *J Neurosurg* 1998, **89:**243–249.

22. Hunter GJ, Hamberg LM, Ponzo JA, *et al.*: **Assessment of cerebral perfusion and arterial anatomy in hyperacute stroke with three-dimensional functional CT: early clinical results.** *Am J Neuroradiol* 1998, **19:**29–37.

23. Baird AE, Benfield A, Schlaug G, *et al.*: **Enlargement of human cerebral ischemic lesion volumes measured by diffusion-weighted magnetic resonance imaging.** *Ann Neurol* 1997, **41:**581–589.

24. Rordorf G, Koroshetz WJ, Copen WA, *et al.*: **Regional ischemia and ischemic injury in patients with acute middle cerebral artery stroke as defined by early diffusion-weighted and perfusion-weighted MRI.** *Stroke* 1998, **29:**939–943.

25.• Stroke Unit Trialists' Collaboration: **Collaborative systematic review of the randomised trials of organised inpatient (stroke unit) care after stroke.** *BMJ* 1997, **314:**1151–1159.

Compared with management of patients with stroke in a general medical ward, the care of patients with stroke by an organized in-patient stroke service resulted in reductions in mortality, dependency, and long-term institutionalization. Length of stay in a hospital or institution was also reduced.

26. Reith J, Jørgensen HS, Pedersen PB, *et al.*: **Body temperature in acute stroke: relation to stroke severity, infarct size, mortality, and outcome.** *Lancet* 1996, **347:**422–425.

27. Weir CJ, Murray GD, Dyker AG, Lees KR: **Is hyperglycaemia an independent predictor of poor outcome after acute stroke? Results of a long term follow up study.** *BMJ* 1997, **314:**1303–1306.

28. Norris JW, Hachinski VC.: **High dose steroid treatment in cerebral infarction.** *BMJ* 1986, **292:**21–23.

29. Norton B, Homer-Ward M, Donnelly MT, *et al.*: **A randomised prospective comparison of percutaneous endoscopic gastrostomy and nasogastric tube feeding after acute dysphagic stroke.** *BMJ* 1996, **312:**13–16.

30. Chen HJ, Lee TC, Wei CP: **Treatment of cerebellar infarction by decompressive suboccipital craniectomy.** *Stroke* 1992, **23:**957–961.

31.• Schwab S, Steiner T, Aschoff A, *et al.*: **Early hemicraniectomy in patients with complete middle cerebral artery infarction.** *Stroke* 1998, **29:**1888–1893.

In this series, hemicraniectomy was performed on 63 patients with complete middle cerebral artery (MCA) territory infarction and was associated with a surprisingly high survival rate of 73%. None of the survivors was wheelchair bound. Suitable patients who may be considered for hemicraniectomy may include patients younger than 70 years of age with massive MCA stroke in the nondominant hemisphere or with only incomplete aphasia before deterioration.

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33.• Hacke W, Schwab S, Horn M, *et al.*: **"Malignant" middle cerebral artery territory infarction: clinical course and prognostic signs.** *Arch Neurol* 1996, **53:**309–315.

In a series of 55 patients with complete middle cerebral artery territory infarction who received intensive care unit treatment, only 12 survived. All deaths were due to transtentorial herniation.

34. Alexandrov AV, Pullicino PM, Meslin EM, Norris JW, for the members of the Canadian and Western New York Stroke Consortiums: **Agreement on disease-specific criteria for do-not-resuscitate orders in acute stroke.** *Stroke* 1996, **27:**232–237.

35. Chiu D, Krieger D, Villar-Cordova C, *et al.*: **Intravenous tissue plasminogen activator for acute ischemic stroke. Feasibility, safety, and efficacy in the first year of clinical practice.** *Stroke* 1998, **29:**18–22.

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37. The Multicenter Acute Stroke Trial–Europe Study Group: **Thrombolytic therapy with streptokinase in acute ischemic stroke.** *N Engl J Med* 1996, **335:**145–150.

38. Multicentre Acute Stroke Trial–Italy (MAST-I) Group: **Randomised controlled trial of streptokinase, aspirin, and combination of both in treatment of acute ischaemic stroke.** *Lancet* 1995, **345:**1509–1514.

39. Donnan GA, Davis SM, Chambers BR, *et al.*: **Streptokinase for acute ischemic stroke with relationship to time of administration.** *JAMA* 1996, **276:**961–966.

40. The NINDS t-PA Stroke Study Group: **Intracerebral hemorrhage after intravenous t-PA therapy for ischemic stroke.** *Stroke* 1997, **28:**2109–2118.

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49. Sherman DG, for the STAT Writers Group: **Defibrinogenation with Viprinex (Ancrod) for the treatment of acute, ischemic stroke [abstract].** *Stroke* 1999, **30:**234.