

*Drug Therapy*ALASTAIR J.J. WOOD, M.D., *Editor***TREATMENT OF ACUTE ISCHEMIC STROKE**

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ISCHEMIC stroke exacts a heavy toll in death and disability worldwide. In the United States, where it is the third leading cause of death and the leading cause of serious long-term disability, approximately 750,000 strokes occur annually, with an annual mortality rate exceeding 150,000.¹⁻⁴

In June 1996, the Food and Drug Administration (FDA) approved tissue plasminogen activator (t-PA) as a safe and effective treatment for stroke if it is given within three hours after the onset of symptoms of stroke.⁵ Subsequently, results of large clinical trials testing the efficacy of antiplatelet, antithrombotic, and neuroprotective treatments appeared. More recently, intraarterial thrombolytic treatment was found to improve the neurologic outcome in patients with occlusion of the middle cerebral artery.⁶ More difficult to evaluate have been approaches to treatment involving integrated stroke-intervention teams and procedures for rehabilitation during the period of convalescence immediately after a stroke. Here, we review data from clinical trials and current treatment options for patients with acute ischemic stroke.

PATHOPHYSIOLOGY AND TARGETS FOR INTERVENTION

Acute ischemic stroke results from the abrupt interruption of focal cerebral blood flow.^{7,8} Angiographically visible embolic or thrombotic occlusions have been identified as the cause of stroke in 70 to 80 percent of patients with symptoms severe enough to warrant early arteriography.^{6,9-11} The rate of visible occlusions is probably lower among all patients with stroke, such as those with mild strokes or classic lacunar syndromes. Other causes of decreased cerebral blood flow include abrupt occlusion of small penetrating arteries and arterioles, single or multiple high-grade arterial stenoses with poor blood flow through collateral vessels, arteritis, arterial dissection, venous occlusion, and profound anemia or profound hyperviscosity.^{12,13}

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The molecular events initiated by acute focal ischemia can be summarized as a time-dependent cascade, characterized by decreased energy production; overstimulation of neuronal glutamate receptors (excitotoxicity); excessive intraneuronal accumulation of sodium, chloride, and calcium ions; mitochondrial injury; and eventual cell death (Fig. 1).^{7,14-16} The fundamental goals of intervention are to restore normal cerebral blood flow as soon as possible and to protect neurons by interrupting or slowing the ischemic cascade.^{7,14,15} Studies using magnetic resonance imaging (MRI) and positron-emission tomography suggest that critical ischemia rapidly produces a core of infarcted brain tissue surrounded by hypoxic but potentially salvageable tissue.^{8,17,18}

EARLY EVALUATION AND SUPPORTIVE TREATMENT

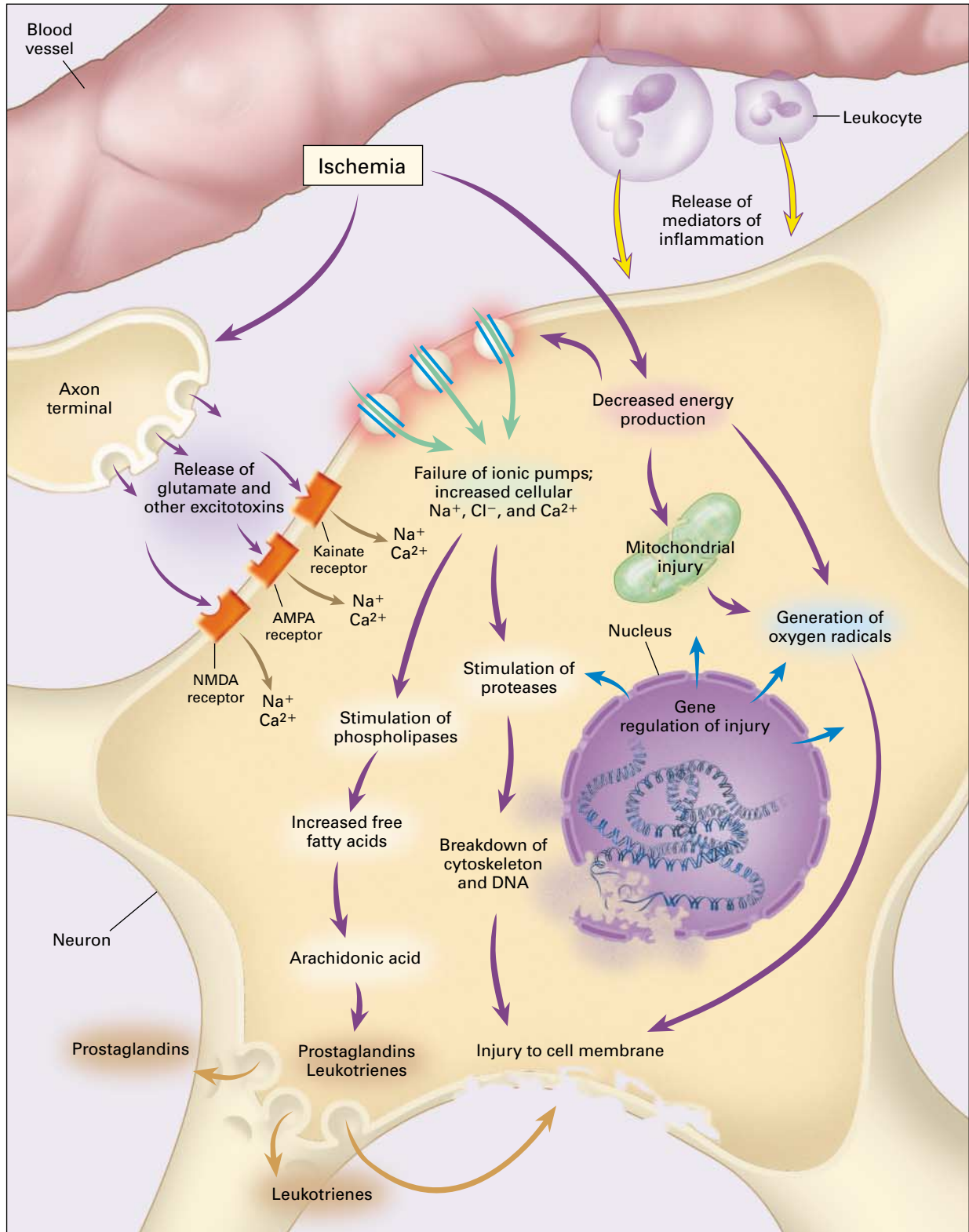
Only about one third of patients who are having a stroke are aware of its symptoms, and most bystanders are not knowledgeable about the signs of stroke. When symptoms or signs are recognized, emergency medical services should be notified.^{19,20} Assessment should begin with evaluation of the patient's airway, breathing, and circulation — the "ABCs" of resuscitation.²¹⁻²⁴ Abnormalities in ventilation or circulation that require immediate intervention are rare at the time of a stroke, as is severe hypertension.²⁵

At the hospital, patients thought to be having a stroke require prompt triage because of the possibility of life-threatening cardiorespiratory effects and of hemorrhagic stroke with associated airway instability.²¹⁻²⁵ The recommended general evaluation includes a history taking; physical examination; measurement of oxygen saturation by pulse oximetry; measurements of serum glucose, electrolytes, and renal function; a complete blood count; coagulation tests; electrocardiography; and chest radiography.

The neurologic examination should include tests for dysphasia, homonymous hemianopia, hemiparesis or hemisensory loss, and other signs of focal injury. The presence of a focal neurologic deficit and a history of abrupt onset of symptoms in the absence of

Figure 1 (facing page). The Molecular Events Initiated in Brain Tissue by Acute Cerebral Ischemia.

Interruption of cerebral blood flow results in decreased energy production, which in turn causes failure of ionic pumps, mitochondrial injury, activation of leukocytes (with release of mediators of inflammation), generation of oxygen radicals, and release of excitotoxins. Increased cellular levels of sodium, chloride, and calcium ions result in stimulation of phospholipases and proteases, followed by generation and release of prostaglandins and leukotrienes, breakdown of DNA and the cytoskeleton, and ultimately, breakdown of the cell membrane. Alteration of genetic components regulates elements of the cascade to alter the degree of injury. AMPA denotes alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid and NMDA *N*-methyl-D-aspartate.



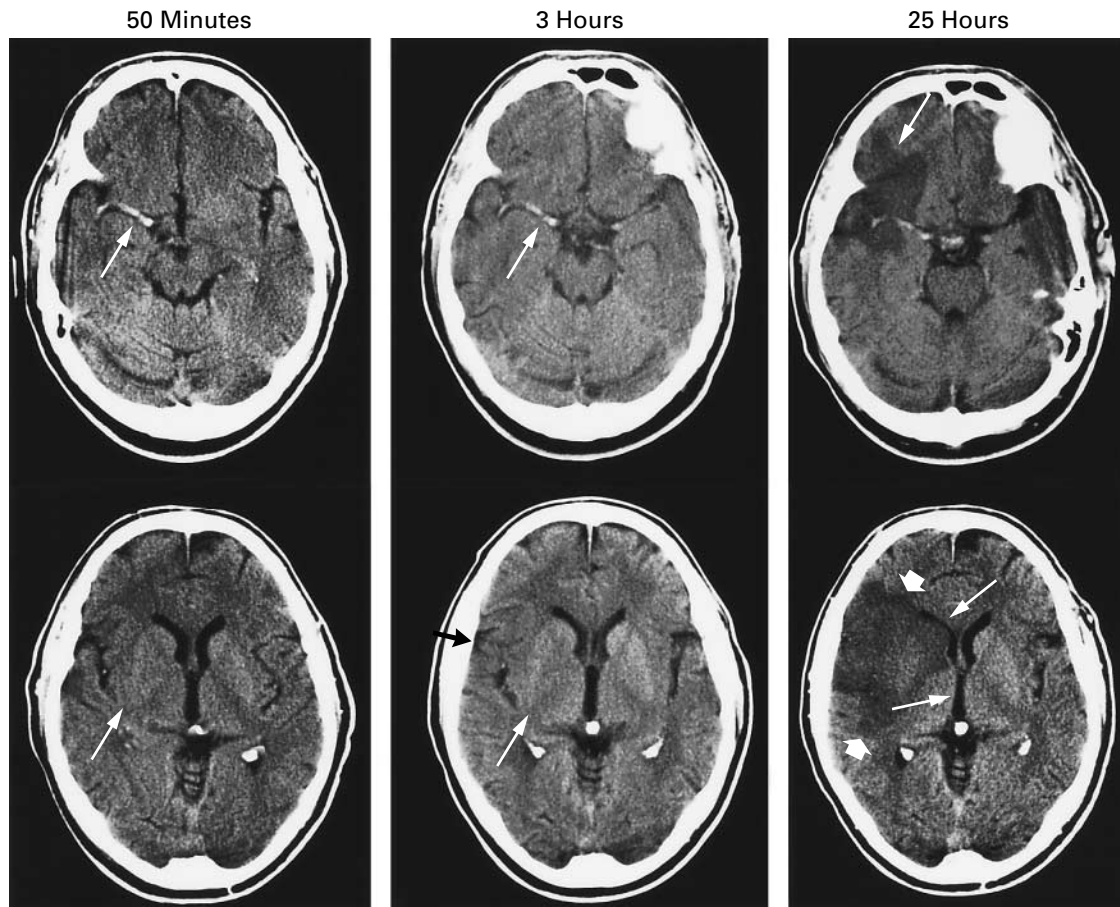


Figure 2. CT Scan of the Brain of a Patient with Confusion, Left Hemiparesis, and Left Hemisensory Loss 50 Minutes, 3 Hours, and 25 Hours after the Onset of Stroke.

For each time point, a lower (top image) and higher (bottom image) axial section is shown. The patient's initial score on the National Institutes of Health Stroke Scale was 18. The patient was treated with intravenous tissue plasminogen activator, at a dose of 0.9 mg per kilogram, beginning two hours after the onset of symptoms. At 50 minutes, a hyperdense thrombus is present in the terminus of the internal carotid artery and in the right middle cerebral artery to the main branch division (arrow, top panel), with possible decreased attenuation of the corpus striatum (arrow, bottom panel). At three hours, hyperdensity of the right middle cerebral artery persists (arrow, top panel); decreased attenuation of the corpus striatum is more conspicuous than before (white arrow, bottom panel); and decreased attenuation of the cerebral cortex, with early swelling of gyri, is now evident (black arrow, bottom panel). At 25 hours, persistent hyperdensity of the right middle cerebral artery indicates that recanalization has failed. Ischemic edema of the frontal operculum and temporal pole is present (arrow, top panel). The ischemic edema involves the corpus striatum, internal capsule, and frontal operculum (wide arrows, bottom panel); the sulci and fissures are effaced, and there is compression of the right frontal horn and anterior third ventricle (narrow arrows).

trauma suggest the occurrence of a stroke. General treatment includes the administration of supplemental oxygen and isotonic intravenous fluids and antipyretic therapy. Diagnostic computed tomography (CT) of the brain should be performed on an urgent basis to differentiate spontaneous intracerebral hemorrhage and subarachnoid hemorrhage from ischemic infarction (Fig. 2).²⁶⁻²⁸ The possibility of encephalitis, or subarachnoid hemorrhage despite an absence of evidence of blood on the CT scan of the brain, warrants lumbar puncture; the possibility of hypoxemia warrants measurements of arterial blood gases; and the possibility of trauma calls for radiography of the cervical

spine in the lateral view. Other conditions that may mimic stroke include hypoglycemia, seizures, a brain tumor, hypertensive encephalopathy, and migraine.

Emboli from the heart account for 10 to 30 percent of all strokes.²⁹ If a cardiac or other systemic disorder is suspected as a cause of or contributing factor in the stroke, a comprehensive evaluation should be performed.^{12,13,22} For example, transesophageal echocardiography has increased the rate of detection of cardiac and aortic causes of embolism.^{29,30}

Early diagnostic testing, in addition to emergency CT studies of the brain, may also include MRI, magnetic resonance angiography, transcranial and extra-

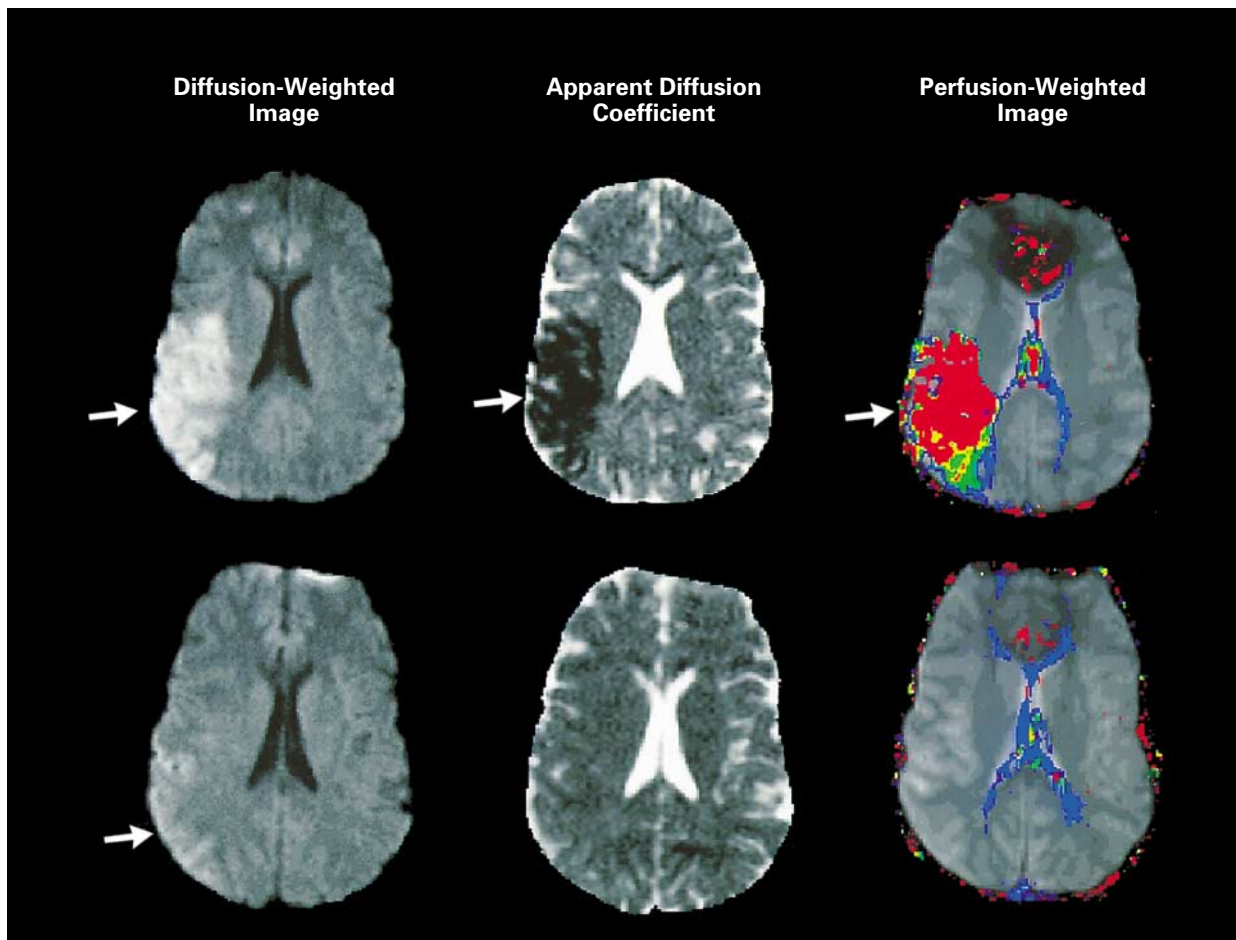


Figure 3. MRI Study Showing Improvements in Diffusion and Perfusion Abnormalities in the Right Cerebral Hemisphere after Intraarterial Administration of Tissue Plasminogen Activator in a 27-Year-Old Woman with Left Hemiparesis.

The top row shows abnormalities (arrows) in a diffusion-weighted image, an image constructed with the apparent diffusion coefficient, and a perfusion-weighted image from a representative scan obtained 2.5 hours after the onset of symptoms, before thrombolytic therapy was begun. In the perfusion-weighted images, red represents a delay in the delivery of the bolus of eight or more seconds, yellow a delay of six to less than eight seconds, green a delay of four to less than six seconds, and blue a delay of two to less than four seconds. Recanalization of the posterior division of the right middle cerebral artery occurred four hours after the onset of symptoms. The bottom row shows corresponding images obtained three hours after vessel recanalization following intraarterial administration of tissue plasminogen activator. A substantial decrease in the size of the lesion (arrow) on the diffusion-weighted image and complete resolution of the lesion on the image constructed with the apparent diffusion coefficient and on the perfusion-weighted image can be seen. The neurologic deficit, as measured by the score on the National Institutes of Health Stroke Scale (on which 0 indicates complete recovery), improved from 14 before thrombolysis to 3 at hospital discharge. (Images courtesy of Chelsea Kidwell, M.D., Jeffrey Saver, M.D., and Jeffrey Alger, Ph.D.)

cranial Doppler ultrasonography, contrast-enhanced helical CT (CT angiography), xenon-enhanced CT, and single-photon-emission CT.^{26,28,31-36} The tests should be selected to establish the anatomical regions and structures involved and the cause of the infarction, since early intervention and subsequent secondary prevention should vary accordingly.

Cerebral arteriography is required if the use of intraarterial thrombolysis is being strongly considered. MRI is appropriate if early assessment is necessary for conditions that may have been missed by the initial CT studies (such as a vertebrobasilar infarction, oc-

clusion of a venous sinus, subdural hematoma, and infarction caused by small-vessel disease).^{26,28} In the near future, diffusion-weighted and perfusion-weighted imaging and cerebral blood-flow imaging during selected MRI examinations should allow more precise identification of early cerebral injury and better characterization of regional cerebral blood flow than is currently feasible. Such techniques may also help guide immediate therapeutic decisions and help physicians assess the response to treatment (Fig. 3).³⁷⁻⁴⁰ Magnetic resonance angiography, Doppler ultrasonography, CT angiography, or cerebral arteriogra-

phy may be used to detect atherosclerotic disease and occlusions of the large arteries, which are often embolic. At least one of these studies in addition to CT is indicated in most patients with stroke; the choice of study depends on the condition of the patient and the extent of the vascular information required.

During the first hours after the onset of symptoms of stroke, treatment of severe hypertension is problematic, because a precipitous decline in arterial pressure may cause harmful decreases in local perfusion.⁴¹ There is no evidence that antihypertensive therapy is beneficial in patients with stroke, even above the blood-pressure treatment thresholds recommended by various consensus panels (systolic pressure thresholds range from >200 to 220 mm Hg, and diastolic pressure thresholds from >110 to 120 mm Hg).^{21-24,42} Initiation of antihypertensive drug therapy is indicated in patients with stroke who have aortic dissection, acute myocardial infarction, heart failure, acute renal failure, or hypertensive encephalopathy and for patients receiving thrombolytic therapy in whom the systolic pressure is 180 mm Hg or higher or the diastolic pressure 105 mm Hg or higher.^{21-24,43} In such patients, the blood pressure should be lowered gradually, and the mean arterial pressure should not be reduced by a total of more than 20 mm Hg.^{21-24,43}

INTRAVENOUS THROMBOLYTIC THERAPY

The results of four phase 3 trials of intravenous t-PA for the urgent treatment of patients with stroke have been reported.⁴⁴⁻⁴⁷ The FDA approved this treatment on the basis of the results of the National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Study (the NINDS rt-PA Stroke Study), in which 624 patients with ischemic stroke were treated with t-PA (0.9 mg per kilogram of body weight, to a maximum of 90 mg) within 3 hours after the onset of symptoms; about half were treated within 90 minutes.^{5,44} The study was carried out in two parts. In part 1, the primary end point was neurologic improvement at 24 hours (as indicated by an improvement of 4 or more points in the score on the 42-point National Institutes of Health Stroke Scale⁴⁸) or complete neurologic recovery; in part 2, the pivotal efficacy trial, the primary end point was the global odds ratio for a favorable outcome, with the use of four measures of complete or near-complete neurologic recovery.

Of the patients treated with t-PA, 31 to 50 percent had a complete or near-complete recovery at three months, as compared with 20 to 38 percent of the patients given placebo,⁴⁴ and the benefit was similar at one year.⁴⁹ The chief hazard of t-PA therapy was symptomatic brain hemorrhage, which occurred in 6.4 percent of the patients given t-PA, as compared with 0.6 percent of those given placebo.^{44,50} However, the mortality rates in the two treatment groups were similar at three months (17 percent in the t-PA

group and 20 percent in the placebo group)⁴⁴ and at one year (24 percent and 28 percent, respectively).⁴⁹ Greater severity of the initial neurologic deficit and evidence of edema or a mass effect on the baseline CT scan were associated with a higher risk of symptomatic intracerebral hemorrhage.⁵⁰

In three other large trials (the European Cooperative Acute Stroke Study [ECASS] I, ECASS II, and the Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke [ATLANTIS] trial), t-PA was not more effective than placebo in improving neurologic outcome at three months.^{45,46,50} In ECASS I, the dose of t-PA was higher (1.1 mg per kilogram) than in the NINDS rt-PA Stroke Study, and intracerebral hematoma was significantly more frequent among patients given t-PA than among those given placebo (19.8 percent vs. 6.5 percent). Among patients with hypoattenuation on CT scanning (indicating edema, infarction, or both) (Fig. 2) that involved more than one third of the territory of the middle cerebral artery, those given t-PA were less likely to have a good outcome than those given placebo, but the numbers of patients in the study were small and the difference did not reach statistical significance.²⁸ In ECASS II and the ATLANTIS trial, in which a combined total of 1413 patients were randomly assigned to receive t-PA (at a dose of 0.9 mg per kilogram) or placebo, symptomatic intracranial hemorrhage occurred in 8.0 percent of the patients treated with t-PA and in 2.4 percent of those given placebo. A post hoc analysis of data on the 800 patients in ECASS II revealed a lower rate of death or dependency among those treated with t-PA than among those treated with placebo.

Three trials of streptokinase were also initiated, but each of them was halted because of an excess rate of poor outcomes or excess mortality among the streptokinase-treated patients.⁵¹⁻⁵³ The dose tested was 1.5 million units, the same as that given to patients with acute myocardial infarction, and treatment was initiated within four to six hours after the onset of symptoms.

In summary, the results of parts 1 and 2 of the NINDS rt-PA Stroke Study support the use of t-PA for the treatment of acute ischemic stroke in patients who meet certain eligibility requirements, if treatment is initiated within three hours after the onset of symptoms (Tables 1 and 2).^{42,44,54} Critics of this approach object that the negative results of some trials may outweigh the positive results of others and that t-PA should not be given unless an occlusive clot is identified.⁵⁵ However, the only clots detected by vascular imaging techniques, including arteriography, are those that occlude large vessels, usually in the setting of cardioembolic or large-vessel occlusive stroke.^{6,10,26} In the NINDS rt-PA Stroke Study, patients with each of the major subtypes of stroke — those with small-vessel occlusive stroke as well as those with cardioembolic and large-vessel occlusive stroke

TABLE 1. CHARACTERISTICS OF PATIENTS WITH STROKE WHO MAY BE ELIGIBLE FOR INTRAVENOUS TISSUE PLASMINOGEN ACTIVATOR THERAPY.*

Age \geq 18 yr
Diagnosis of ischemic stroke causing clinically apparent neurologic deficit
Onset of symptoms $<$ 3 hr before possible beginning of treatment
No stroke or head trauma during the preceding 3 mo
No major surgery during the preceding 14 days
No history of intracranial hemorrhage
Systolic blood pressure \leq 185 mm Hg
Diastolic blood pressure \leq 110 mm Hg
No rapidly resolving symptoms or only minor symptoms of stroke
No symptoms suggestive of subarachnoid hemorrhage
No gastrointestinal or urinary tract hemorrhage within the preceding 21 days
No arterial puncture at a noncompressible site within the preceding 7 days
No seizure at the onset of stroke
Prothrombin time \leq 15 sec or international normalized ratio \leq 1.7, without the use of an anticoagulant drug
Partial-thromboplastin time within the normal range, if heparin was given during the preceding 48 hr
Platelet count \geq 100,000/mm ³
Blood glucose concentration $>$ 50 mg/dl (2.7 mmol/liter)
No need for aggressive measures to lower blood pressure to within the above-specified limits

*Data are from Adams et al.⁴² and the National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Study Group.⁵⁴

— benefited from therapy.^{44,56,57} Although the diagnoses of subtypes of stroke in the emergency department may not have been accurate in this study and although the numbers were small, a specific diagnosis, though intuitively appealing, was not found to be necessary.⁵⁶⁻⁵⁸ More important, the negative results of ECASS I, ECASS II, and the ATLANTIS trial involved patients with stroke who were treated much later than were those in the NINDS rt-PA Stroke Study. Only 14 percent of the patients in the trials with negative results were treated within 3 hours, and even fewer were treated within 90 minutes after the onset of stroke. In the NINDS rt-PA Stroke Study, all but 2 of the 624 patients were enrolled within 3 hours, and 48 percent of them were enrolled within 90 minutes.

A recent case series indicated that implementation of intravenous t-PA therapy may not always be easy and safe, but in other series the safety and efficacy of this treatment were similar to those in both parts of the NINDS rt-PA Stroke Study.⁵⁹⁻⁶⁷ In addition, intravenous t-PA was found to be cost effective in an analysis of the patients in the NINDS rt-PA Stroke Study.⁶⁸

INTRAARTERIAL THROMBOLYTIC THERAPY

Local intraarterial thrombolysis performed with a microcatheter that is placed into, beyond, and prox-

TABLE 2. TREATMENT OF ISCHEMIC STROKE WITH INTRAVENOUS TISSUE PLASMINOGEN ACTIVATOR (t-PA).*

Determine the patient's eligibility for treatment (Table 1).
Infuse t-PA at a dose of 0.9 mg/kg (maximum, 90 mg) over a 60-min period with the first 10 percent of the dose given as a bolus over a 1-min period.
Perform neurologic assessments every 15 min during infusion of t-PA, every 30 min for the next 6 hr, and every 60 min for the next 16 hr.† If severe headache, acute hypertension, or nausea and vomiting occur, discontinue the infusion and obtain an emergency CT scan.
Measure blood pressure every 15 min for 2 hr, every 30 min for 6 hr, and every 60 min for 16 hr; repeat measurements more frequently if systolic pressure is $>$ 180 mm Hg or diastolic pressure is $>$ 105 mm Hg, and administer antihypertensive drugs as needed to maintain blood pressure at or below those levels.

*Data are from Adams et al.⁴² and the National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Study Group.⁵⁴

†For this level of monitoring, admission to an intensive care unit or a stroke unit is recommended.

imal to an arterial occlusion (Fig. 4) is in use worldwide on the basis of the results of two randomized trials and numerous case series.^{6,9,69-85} In the past, the agent most commonly studied was urokinase; intraarterial t-PA and prourokinase have mainly been used in recent investigational studies. Approximately 40 percent of the patients who undergo this treatment have complete arterial recanalization, and approximately 35 percent have partial recanalization.^{6,9,69-85} These rates of recanalization are higher than those that have been reported for patients who undergo intravenous thrombolytic therapy.^{11,86,87}

The larger of the two randomized trials, the Prolyse in Acute Cerebral Thromboembolism II (PROACT II) trial,⁶ included patients with arteriographically confirmed occlusion of the middle cerebral artery or a first-order branch of it. Of the 12,323 patients who were screened, 474 underwent arteriography, and 180 were enrolled; 121 received local intraarterial prourokinase and low-dose intravenous heparin within six hours after the onset of symptoms, and 59 received only low-dose intravenous heparin during this period. At two hours, there was partial or complete lysis in 67 percent of the patients in the prourokinase group, as compared with 18 percent of those in the heparin-only group ($P<0.001$). In addition, prourokinase was more effective than placebo in achieving clot lysis in the smaller of the two trials, which included 40 patients.⁹ The primary outcome of the PROACT II trial was the ability to live independently at three months after the stroke, an outcome that was attained by 40 percent of the patients treated with prourokinase and heparin as compared with 25 percent of those treated with heparin alone ($P=0.04$). After treatment, intracerebral hemorrhage with neurologic deterioration occurred in

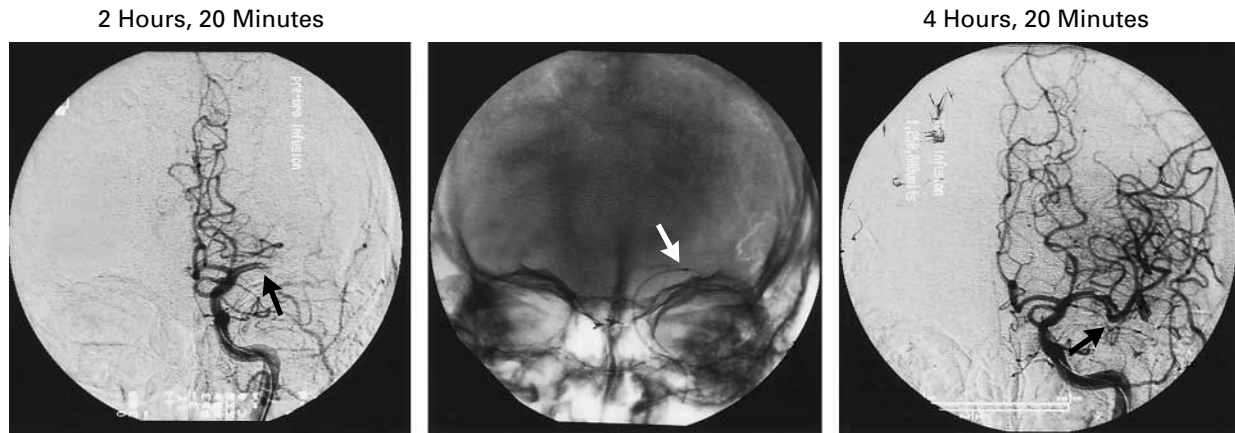


Figure 4. Cerebral Arteriograms in a Patient with Dysphasia and Right Hemiplegia.

A cerebral arteriogram shows the placement of the microcatheter tip just proximal to the embolic occlusion in the trunk of the left middle cerebral artery (arrow, left-hand panel). Intraarterial administration of urokinase was initiated 2 hours and 20 minutes after the onset of symptoms. The center panel shows the position of the microcatheter after infusion of 1.25 million IU of urokinase over a two-hour period (arrow). The final cerebral arteriogram (right-hand panel) demonstrates complete recanalization of the left middle cerebral artery. The microcatheter tip can be seen at the distal end of the trunk of the right middle cerebral artery (just proximal to the arrow). (Arteriograms courtesy of Thomas Tomsick, M.D.)

10 percent of the patients in the prourokinase group and in 2 percent of those in the heparin-only group ($P=0.06$).

PROACT II was the first randomized trial in which intraarterial thrombolysis was shown to have a benefit in patients who have had a stroke caused by occlusion of the middle cerebral artery and in patients whose treatment is initiated more than three hours after the onset of symptoms. The results of case studies comparing intraarterial urokinase with intraarterial t-PA and the preliminary results of a study of intravenous t-PA in combination with intraarterial t-PA suggest that early intraarterial therapy with urokinase or t-PA may also be effective.^{69-81,88} Intraarterial thrombolysis has not been directly compared with intravenous thrombolysis, so the relative merits of these two routes of therapy in patients with acute ischemic stroke are unknown. In patients with possible middle-cerebral-artery occlusion, we recommend intravenous thrombolysis with t-PA if treatment can be initiated within three hours after the onset of symptoms; intraarterial thrombolysis may be justified in these patients if treatment is to begin three to six hours after the onset of symptoms. If treatment can be given within three hours, we consider intraarterial thrombolysis in patients in whom there is a strong possibility of occlusion of the middle cerebral artery (for example, patients in whom a thrombus is identified in the main trunk of this artery on brain CT or CT angiography).

No randomized trials of thrombolytic treatment for vertebrobasilar stroke have been completed. A recent small case series suggested a possible benefit of intravenous t-PA if treatment is initiated within three

hours after symptoms appear.⁶⁷ Because of the very poor outcome among patients with basilar-artery occlusion and the reported good recovery after intraarterial therapy initiated more than six hours after the onset of symptoms, cerebral arteriography performed on an emergency basis, followed by intraarterial thrombolysis during the three-to-six-hour period, can be recommended in patients with basilar-artery occlusion who are judged to have a poor prognosis.^{71,72,77,79,80}

ANTITHROMBOTIC AND ANTIPLATELET DRUGS

Patients with ischemic stroke caused by embolism from the heart or with less common disorders — such as the antiphospholipid-antibody syndrome, cerebral venous-sinus thrombosis, extracranial carotid-artery dissection or vertebral-artery dissection, the intraluminal-clot syndrome, and tight intracranial large-artery stenosis — are often treated with intravenous heparin followed by warfarin.^{21-24,89-94} No data from clinical trials are available to validate this treatment for stroke, despite its theoretical appeal. In addition, because of the associated risk of hemorrhage in the ischemic area, there is no consensus on the best time to start anticoagulant therapy.^{22-24,95,96}

Heparin

In the International Stroke Trial, 19,435 patients with ischemic stroke were randomly assigned to receive subcutaneous heparin at a dose of 5000 or 12,500 IU twice daily or no heparin, with or without 300 mg of aspirin per day, within 48 hours after the onset of symptoms.⁹⁷ There were no differences among the treatment groups in the primary outcome

(death within 14 days or death or dependency at 6 months). Among the patients who received heparin, there was a significant 0.9 percent reduction in the absolute risk of recurrent ischemic stroke during the first 14 days, an effect that was counterbalanced by a significant 0.8 percent increase in the absolute risk of hemorrhagic stroke. Hemorrhagic complications, including the need for transfusion, fatal extracranial bleeding, and hemorrhagic stroke, were associated with the high-dose regimen of heparin, but the activated partial-thromboplastin time was not monitored, and one third of the patients were treated before a CT scan of the head was obtained to rule out the possibility of brain hemorrhage. The results of the low-dose regimen of heparin were more encouraging, with a significant 1.2 percent decrease in the absolute risk of death or nonfatal recurrent stroke at 14 days and with a rate of hemorrhagic complications in the same range as with aspirin alone.

Three trials of low-molecular-weight heparin in patients with acute ischemic stroke have been completed. In one, administration of nadroparin calcium or placebo was started within two days after the onset of stroke in 312 patients; more patients in the nadroparin group recovered.⁹⁸ These results were not confirmed in a larger trial, which involved 750 patients.⁹⁹ In a placebo-controlled trial of another low-molecular-weight heparin, danaparoid, in which 1281 patients were treated within 24 hours after the onset of stroke, there was no difference in the rate of recurrence or progression of stroke between those who received the drug and those who received placebo.¹⁰⁰ Subgroup analysis did suggest a potential benefit of danaparoid in patients with occlusion or severe stenosis of the internal carotid artery.¹⁰¹ A meta-analysis of data from trials of early treatment with anticoagulant drugs for patients with acute ischemic stroke suggests no clinical benefit with such treatment.^{95,102}

Aspirin

Early treatment with aspirin was evaluated in three trials in which more than 40,000 patients were treated within 48 hours after the onset of symptoms. In the International Stroke Trial, there were no differences among patients treated with aspirin, heparin, or neither of these drugs in the rate of death within 14 days or death or dependency at 6 months.⁹⁷ Secondary analyses revealed a significant decrease in the rate of recurrence of ischemic stroke at two weeks among the patients treated with aspirin (2.8 percent, vs. 3.9 percent among those not treated with aspirin). However, there were no differences among the groups in the combined end point of severe disability and death.

In the Chinese Acute Stroke Trial, in which 160 mg of aspirin or placebo was given daily for four weeks to 21,106 patients with acute ischemic stroke, the mortality rate at one month in the aspirin group was slightly but significantly lower than that in the

placebo group (3.3 percent vs. 3.9 percent), but there was no difference between the groups in the overall rate of death or severe disability.¹⁰³ As in the International Stroke Trial, the rate of recurrent ischemic stroke in the aspirin group was lower than that in the placebo group at one month (1.6 percent vs. 2.1 percent), as was the rate of death or nonfatal recurrent stroke (5.3 percent vs. 5.9 percent). A combined analysis of the results of the International Stroke Trial and the Chinese Acute Stroke Trial suggested that early death, recurrent stroke, or late death can be prevented in 1 patient with acute stroke by giving aspirin to 100 patients with acute stroke.¹⁰⁴

Urgent treatment with aspirin was studied in the Multicentre Acute Stroke Trial–Italy, in which 622 patients were randomly assigned within six hours after the onset of symptoms to receive aspirin, intravenous streptokinase, both of these drugs, or neither of them. There were no differences among the treatment groups with respect to the primary outcome, which was death or severe disability at six months.^{53,105}

Ancrod

Ancrod converts fibrinogen into soluble fibrin products, with a subsequent decrease in plasma concentrations of fibrinogen and depletion of the substrate needed for thrombus formation.¹⁰⁶ In a trial of 500 patients randomly assigned to receive ancrod or placebo within three hours after the onset of symptoms, total or near-total recovery at three months was achieved in 42 percent of the patients given ancrod, as compared with 34 percent of those given placebo ($P=0.04$).¹⁰⁷

In summary, the results of trials of antithrombotic and antiplatelet drugs in patients with acute ischemic stroke confirm that aspirin at doses of 160 to 325 mg per day has a moderate benefit in preventing new vascular events. In contrast, studies do not support the routine use of high-dose subcutaneous heparin or intravenous low-molecular-weight heparin. Administration of low-dose subcutaneous heparin (5000 IU twice daily) is safe and can prevent deep-vein thrombosis in patients with stroke.^{22,97} Ancrod may increase the chance of total or near-total recovery in patients with stroke.

NEUROPROTECTION

There has been much interest in drugs that may protect neurons from the effects of ischemia, but several drugs that seemed promising in experimental studies or in small trials (including naloxone, gangliosides, nimodipine, *N*-methyl-D-aspartate–receptor antagonists, antibodies to adhesion molecules, and free-radical scavengers) have proved ineffective in phase 3 trials.^{15,108,109} The observed lack of efficacy of these drugs may be due to delays in the initiation of treatment, inadequate doses, inadequate drug pen-

etration, adverse effects, or insufficient matching of a drug's mode of action to the mechanism of brain injury.^{15,108,110} For example, thrombotic, embolic, and small-vessel strokes may all involve the deep white matter, where no synapses are found. Thus, it is unlikely that a neuroprotective drug that acts at the synaptic level, such as an *N*-methyl-D-aspartate-receptor antagonist, would be effective in protecting ischemic white matter. Perhaps even more important, arterial occlusion and inadequate circulation in collateral vessels may preclude adequate delivery of the drug to a substantial portion of the ischemic tissue.

TREATMENT IN THE HOSPITAL

Patients with stroke may be hospitalized in an intensive care unit, a general medical unit, or an integrated stroke unit.²⁴ Patients receiving thrombolytic therapy should be hospitalized in an intensive care unit or a specialized stroke unit capable of performing frequent assessments during the first 24 to 36 hours after the onset of stroke (for example, to allow early detection of brain hemorrhage) (Table 2).^{42,50} Patients whose neurologic or medical condition is unstable should also be hospitalized in an intensive care unit.

Approximately half the deaths attributable to stroke are the result of medical complications, such as pneumonia and sepsis, and half are attributable to neurologic complications, such as new cerebral infarction and cerebral edema.¹¹¹ Fever should prompt an investigation into the possibility of infection. Because fever may be harmful, regardless of its cause, an antipyretic drug should be given, and more aggressive measures (such as the use of a cooling blanket to achieve normothermia) may be justified in certain patients.^{22,112-114} Patients with cardiac disease and those thought to be at risk for serious arrhythmia require continuous cardiac monitoring and frequent cardiac assessments.^{22,24} Seizures may occur in 5 percent or more of patients with ischemic stroke; they require anticonvulsant drug therapy.^{22,115}

Measures to encourage mobility and nutrition and to minimize complications (which may include deep-vein thrombosis, pulmonary embolism, pneumonia, urinary tract infection, and decubitus ulcers) should be initiated as appropriate to the patient's neurologic deficit and coexisting medical conditions.^{22,24,111,116} For example, abnormalities in swallowing are common, and so patients with abnormalities of speech or of facial, buccal, or lingual movements should undergo a formal evaluation of swallowing, if possible, to guide nutrition and to minimize the risk of aspiration.^{117,118} Deep-vein thrombosis can be prevented by intermittent pneumatic compression of the legs and the use of elastic stockings, aspirin, low-molecular-weight heparin, or low-dose subcutaneous heparin (5000 IU twice daily).^{22,97,119-121}

The neurologic deficit resulting from ischemic

stroke and the vascular cause of the stroke, if determined, should guide the frequency of neurologic assessments and subsequent interventions. Patients receiving intravenous or intraarterial thrombolytic therapy should be examined often (Table 2), as should patients at risk for progressive ischemia (for example, those with large-vessel occlusion and poor flow through collateral vessels) and patients at risk for life-threatening cerebral edema (for example, those with a very large infarction of the cerebral hemisphere or infarction of the cerebellum).^{24,42} Signs of increasing cerebral edema and elevated intracranial pressure include a decline in the level of consciousness, loss of spontaneous venous pulsations on ophthalmoscopic examination, enlargement of the pupil ipsilateral to the infarcted hemisphere, progression of the focal neurologic deficit, and corticospinal signs (such as weakness or hyperreflexia) on the side that was not initially affected by the stroke.^{122,123} Development of these signs should prompt a thorough medical evaluation and urgent CT of the brain. In patients thought to be at very high risk for cerebral edema, such as those with severe neurologic deficits or signs of early edema on CT scanning at the time of admission, radiographic evidence of progressing cerebral edema may precede the appearance of clinical signs.¹²³ Repeated imaging of the brain may be needed in such patients to allow a more timely diagnosis.

If potentially life-threatening cerebral edema is identified, osmotic diuresis with mannitol can be effective (25 to 50 g given intravenously every three to five hours, to a maximal dose of 2 g per kilogram per day).^{22,24,124-126} Furosemide, given intravenously in doses of 20 to 80 mg every 4 to 12 hours, can be used to supplement the effects of mannitol.¹²⁶ Replacement fluids can be given to maintain the calculated serum osmolality at 300 to 320 mOsm per kilogram of water. Glucocorticoids are not recommended and may be harmful.²² If signs of edema persist or progress, intubation and mechanical hyperventilation to achieve a partial pressure of carbon dioxide of 25 to 30 mm Hg can temporarily lower the intracranial pressure.^{22,126}

Medical treatment of cerebral edema and increased intracranial pressure may be ineffective. Surgical decompression can be lifesaving for patients with an infarction of the cerebellum or a large infarction of the cerebral hemisphere.^{22,127,128}

INTEGRATED STROKE-INTERVENTION TEAMS AND STROKE UNITS

In the NINDS rt-PA Stroke Study, specially trained technicians, nurses, and physicians were organized into integrated stroke-intervention teams.^{49,129} The integrated-team approach can increase the number of patients treated rapidly, permit closer monitoring of patients, potentially increase the safety of thrombolysis, and streamline diagnosis and therapy.^{49,68}

The stroke-unit approach involves a continuum of

care beginning at or shortly after hospital admission and continuing beyond the period of acute medical care and through the initial stages of rehabilitation.¹³⁰⁻¹³⁵ The results of randomized trials and meta-analyses indicate that short-term and long-term mortality rates are lower, hospitalization shorter, and the likelihood of discharge to the home greater among patients treated in integrated stroke units than among those treated in general medical units.¹³⁰⁻¹³⁵ In these randomized studies, the length of stay in an inpatient setting was two to five weeks; as a result, those studies do not provide definitive guidance for the care of patients with stroke, because for most patients, general medical care and brief rehabilitation are followed by early discharge (to the home, a rehabilitation unit, or an extended-care facility).^{68,136}

REHABILITATION

From half to two thirds of patients who survive a stroke regain independence, and up to 80 percent of these patients retain or regain the ability to walk.¹³⁷ The role of rehabilitation services in promoting recovery after stroke was systematically reviewed by a multidisciplinary consensus panel, which examined more than 1900 clinical research articles.^{137,138} The panel made the following four recommendations, each supported by results from two or more randomized trials. First, diagnostic evaluation, initial treatment, preventive therapy, and rehabilitation services should be provided in a coordinated setting. Second, measures to prevent deep-vein thrombosis should be implemented. Third, prevention of recurrent stroke and of complications of stroke should be given high priority. Fourth, surveillance for the development of depression is important, since major depression occurs in 10 to 30 percent of patients who survive a stroke.¹³⁸⁻¹⁴⁰ It was also recommended (though with less support from clinical studies) that the following problems be assessed and treated: dysphagia, urinary incontinence, immobility, focal weakness, aphasia, a tendency to fall, injury to the skin, bowel irregularity or fecal incontinence, and shoulder injury.^{137,138,141} The rationale for intensive rehabilitation programs and criteria for the selection of patients for such programs were also provided.^{138,142} Early initiation of rehabilitation services may increase the potential for improved functional outcome.¹⁴³

CONCLUSIONS

Safe and effective treatment is now available for patients with acute ischemic strokes. Intravenous thrombolysis with t-PA is safe and improves outcome if treatment is initiated within three hours after the onset of symptoms. Intraarterial revascularization may provide more complete restitution of flow in the middle cerebral artery than intravenous thrombolytic therapy. Intraarterial therapy may also improve the clinical outcome if it can be undertaken within the

first six hours after the onset of symptoms. Anti-thrombotic drugs lessen the likelihood of deep-vein thrombosis, and aspirin offers a moderate benefit in the prevention of recurrent stroke. Finally, advances in the understanding of the rehabilitation process and its implementation will continue to produce improvements in both short-term and long-term quality of life among patients who survive a stroke.

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