CLINICAL PRACTICE

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Acute Ischemic Stroke

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

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A 62-year-old, right-handed, independently functioning man presents 1 hour after a sudden, witnessed onset of speech difficulty and right-sided numbness and weakness. He is alert with moderate aphasia, facial weakness on the right side, and weakness in the right arm and leg with decreased sensation to light touch. His blood pressure is 160/95 mm Hg, plasma glucose level 79 mg per deciliter (4.4 mmol per liter), and body temperature 37.2°C. His medical history is unremarkable, and he is taking no medications. Noncontrast computed tomography (CT) of the head shows slight hypodensity in the left insular cortex (Fig. 1A). What would you do?

THE CLINICAL PROBLEM

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Each year in the United States, approximately 700,000 people have an acute ischemic stroke.[1] Before modern treatments, early mortality was 10%.[2] Among survivors, one half had moderate-to-severe neurologic deficits, and a quarter were dependent on others.[3] The introduction of intravenous alteplase in 1995 led to substantial improvement in outcomes.[4] More recently, effective mechanical thrombectomy has radically altered initial management in many patients.[5] Understanding treatment options for acute ischemic stroke is important to ensure prompt administration of appropriate care or referral.

STRATEGIES AND EVIDENCE

Treatment for patients with acute ischemic stroke is guided by the time from the onset of stroke, the severity of neurologic deficit, and findings on neuroimaging. By convention, the time of stroke onset is established as the time that the patient was last known to be well (i.e., in normal or baseline state, as confirmed by medical history). For persons who awake with stroke, this time will be sometime before they went to sleep. The severity of neurologic deficit is measured by means of the National Institutes of Health Stroke Scale (NIHSS), on which scores range from 0 to 42, with lower numbers indicating milder deficits.[6] Deficit severity is further characterized as nondisabling or disabling if it would prevent performance of basic activities of daily living or return to work.

INITIAL EVALUATION AND IMAGING

Rapid onset of neurologic deficits localized to a single cerebral arterial vascular territory is the archetypal clinical presentation of acute ischemic stroke. The blood glucose level should be measured routinely to exclude hypoglycemia. Brain imaging is necessary to rule out intracerebral hemorrhage; noncontrast CT is preferred be-

KEY CLINICAL POINTS

ACUTE ISCHEMIC STROKE

- Treatment for patients with acute ischemic stroke is guided by the time from the onset of stroke, the severity of neurologic deficit, and findings on neuroimaging. By convention, the time of stroke onset is established as the time that the patient was last known to be well (i.e., in a normal or baseline state, as confirmed by medical history).
- Intravenous thrombolysis with alteplase (a recombinant tissue plasminogen activator) improves outcomes in selected patients with acute ischemic stroke when administered within 4.5 hours after onset. Later treatment may improve outcomes in selected patients, with the treatment window extended to 9 hours from onset.
- Intraarterial catheter-based mechanical thrombectomy of occluded large intracranial arteries improves outcomes in selected patients with acute ischemic stroke when performed up to 24 hours after onset.
- The benefit of alteplase and mechanical thrombectomy is time-dependent, so assessment and treatment should be instituted rapidly.
- In selected patients with mild acute ischemic stroke who do not qualify for intravenous thrombolysis or mechanical thrombectomy, dual antiplatelet therapy with clopidogrel and aspirin when administered within 24 hours after onset and continuedfor 21 days lowers the risk of recurrent stroke.

cause of its availability, rapidity, and high sensitivity. Magnetic resonance imaging (MRI) with special sequences can also be used.[5] In clinically typical cases, a noncontrast CT that shows no other explanation for the neurologic deficit is sufficient to diagnose acute ischemic stroke on initial imaging; diffusion-weighted MRI is not necessary. Because the benefits of treatment for acute stroke are time-sensitive, initial diagnostic imaging should be performed quickly.

Further neuroimaging may be required to determine eligibility for some interventions. Noncontrast CT is used to determine the Alberta Stroke Program Early Computed Tomography Score (ASPECTS; scores range from 0 to 10 on the basis of ischemic changes in the territory of the middle cerebral artery, with 0 indicating the most extensive ischemic changes).[7] Diffusion-weighted MRI and perfusion CT measurements are used to define ischemic brain tissue that is probably irreversibly damaged ("core"). Delayed arrival of contrast, as shown on perfusion MRI or perfusion CT, is used to define ischemic tissue that is potentially salvageable ("penumbra"). MR angiography (MRA) and CT angiography (CTA) show the location of intracranial arterial occlusions (Fig. 1B).[8,9] In patients with renal insufficiency, time-of-flight MRA (which does not use contrast) can be used to identify arterial occlusions and inform therapeutic decisions.

MEASUREMENT OF RESPONSE TO TREATMENT

Clinical benefit is conventionally measured with the use of the modified Rankin scale, on which scores range from 0 (no symptoms) to 6 (death). A score of 1 indicates an ability to carry out all usual duties and activities despite symptoms. A score of 2 indicates an inability to carry out all normal activities but an ability to look after one's own affairs without assistance.[10]

TREATMENT OPTIONS

Alteplase within 4.5 Hours after Stroke Onset

Randomized, controlled trials have shown that intravenous administration of alteplase (at a dose of 0.9 mg per kilogram of body weight over 60 minutes [maximum total dose, 90 mg], with the first 10% of the dose given as a single bolus over 1 minute) within 4.5 hours after the onset of stroke reduces disability from acute ischemic stroke.[11] Intravenous alteplase has shown benefit for patients with disabling stroke regardless of the NIHSS score; it is not recommended for those with nondisabling stroke and an NIHSS score of 0 to 5, for those with associated conditions in which the bleeding risk is excessive, or for those with CT evidence of extensive irreversible injury. Intravenous alteplase is considered a first-line agent in eligible patients.[5]

Before the administration of alteplase, no neuroimaging other than initial diagnostic noncontrast CT is necessary. Given the low prevalence of unsuspected coagulopathies, intravenous alteplase should be administered while the results of hematologic tests are pending if there is no reason to suspect an abnormality. On the basis of the National Institute of Neurological Disorders and Stroke (NINDS) trial protocol for

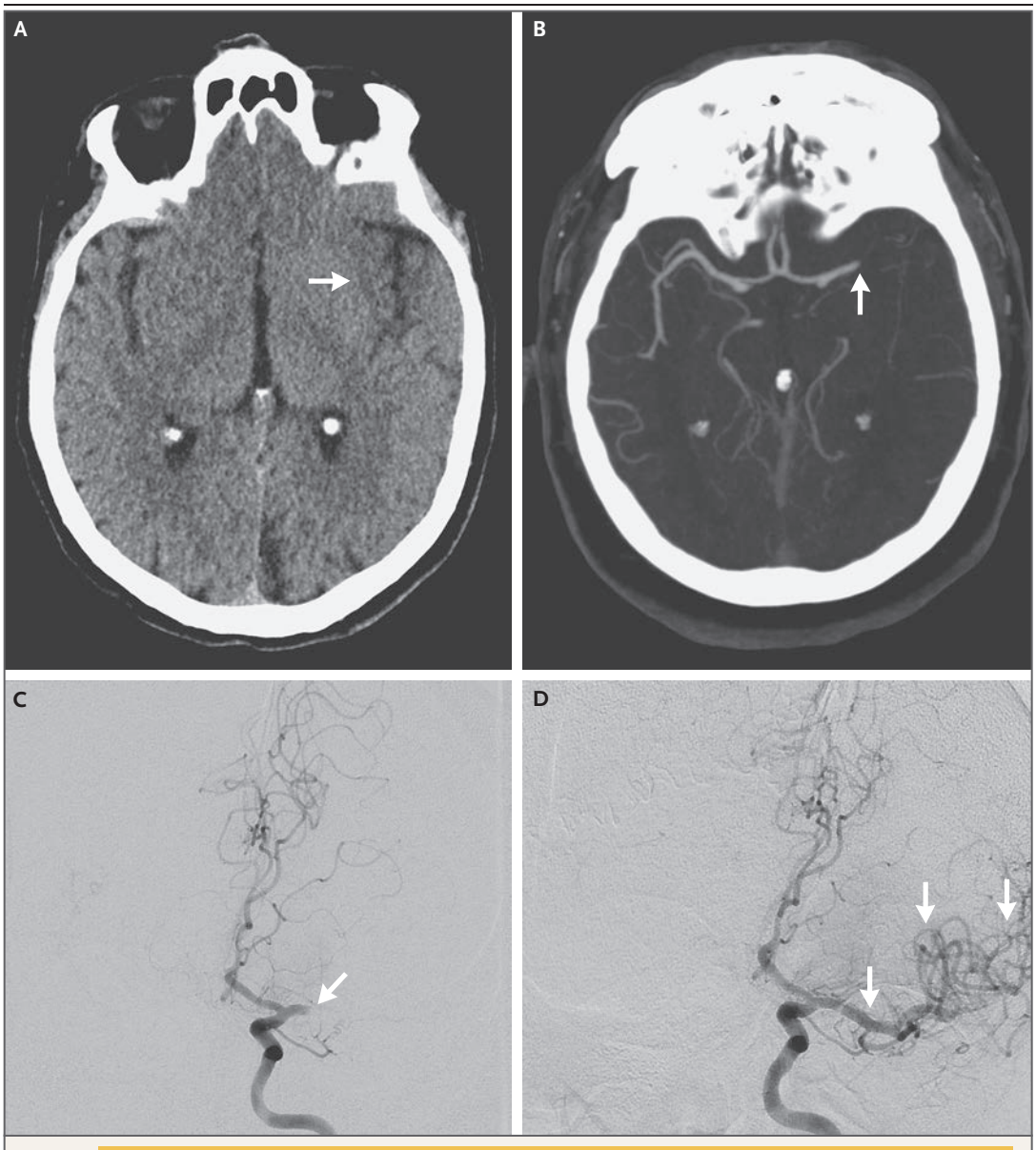


Figure 1. Neuroimaging from Patients with Acute Ischemic Stroke and Occlusion of the Left Middle Cerebral Artery.

Panel A shows a noncontrast computed tomographic (CT) scan of the head (transverse section) revealing slight hypodensity in the left insular cortex (arrow). Panel B shows a CT angiogram (transverse section) revealing an occlusion of the first segment of the left middle cerebral artery (arrow). Panel C shows a cerebral arteriogram (anterior projection) revealing an occlusion of the first segment of the middle cerebral artery before mechanical thrombectomy (arrow). Panel D shows a cerebral arteriogram (anterior projection) revealing recanalization of the left middle cerebral artery after thrombectomy (arrows).

the use of tissue plasminogen activator,[4] the blood pressure must be lower than 185/110 mm Hg before and during infusion and lower than 180/105 mm Hg for at least the first 24 hours afterward. Patients who have received intravenous alteplase are admitted to an intensive care unit or specialized stroke unit for close neurologic monitoring and blood-pressure control, if necessary.

The benefit of intravenous alteplase is time-dependent. In a meta-analysis of nine randomized, controlled trials,[11] 32.9% of the patients in

the alteplase group, as compared with 23.1% of the patients in the control group, had a favorable 3-month outcome (defined as a modified Rankin scale score of 0 or 1) when treatment was administered within 3 hours after the onset of stroke (adjusted odds ratio, 1.75; 95% confidence interval [CI], 1.35 to 2.27); the corresponding rates were 35.3% and 30.1% when treatment was administered between 3 and 4.5 hours after onset (adjusted odds ratio, 1.26; 95% CI, 1.05 to 1.51). Large intracerebral hemorrhage occurred in 6.8% of the patients in the alteplase group and in 1.3% of those in the control group. The overall outcomes, as assessed by the modified Rankin scale, among the patients in the alteplase group reflected the deleterious effects of hemorrhage along with the beneficial effect on ischemic stroke recovery.

Alteplase at More Than 4.5 Hours after Stroke Onset

In the WAKE-UP (Efficacy and Safety of MRI-based Thrombolysis in Wake-Up Stroke) trial, 503 patients with a time of onset of disabling acute ischemic stroke that was unclear, but greater than 4.5 hours from the time last known to be well (94% of whom awoke with stroke), were randomly assigned to receive intravenous alteplase at a standard dose or placebo administered within 4.5 hours after the recognition of stroke symptoms.[12] Patients were eligible if they had an abnormal signal on diffusion-weighted MRI, no visible signal change on fluid-attenuated inversion recovery imaging, a lesion on diffusion-weighted MRI that was not larger than one third of the territory of the middle cerebral artery, an NIHSS score of 25 or lower, and no planned thrombectomy. More participants in the alteplase group than in the placebo group attained the primary end point of a modified Rankin scale score of 0 or 1 at 90 days (53% vs. 42%; adjusted odds ratio, 1.61; 95% CI, 1.09 to 2.36).

Data from randomized, controlled trials that used imaging eligibility criteria support a benefit of late administration of intravenous alteplase (4.5 to 9.0 hours after the onset of stroke or measured from the mid-point of sleep). In a pooled analysis of patients with a penumbra-to-core ratio of greater than 1.2 and a core volume of less than 70 ml (as shown on perfusion CT or diffusion-weighted MRI with perfusion MRI), a greater percentage of those in the alteplase group than in the control group had a good outcome (defined as a modified Rankin scale score of 0 or 1) at 90 days (36% vs. 29%; adjusted odds ratio, 1.86; 95% CI, 1.15 to 2.99).[13] Enrolled patients had much larger penumbra-to-core ratios and lower core volumes than the limits set by eligibility criteria (a mean penumbra volume of 63.9 ml and a mean core volume of 8.0 ml in the alteplase group). In health care settings where mechanical thrombectomy is not available, patients who are within the treatment window of 4.5 to 9.0 hours can be considered for intravenous alteplase on the basis of the characteristics of the patients enrolled in these trials. However, mechanical thrombectomy is preferred when available.

Mechanical Thrombectomy within 6 Hours after Stoke Onset

Mechanical thrombectomy entails passing an intraarterial catheter from a peripheral puncture into an intracranial artery and removing an occluding thrombus by ensnaring it or by suction (Fig. 1C and 1D). Mechanical thrombectomy, performed within 6 hours after the onset of stroke, is another first-line treatment for selected patients on the basis of multiple randomized, controlled trials that have shown a benefit. These trials primarily enrolled patients 18 years of age or older who had a prestroke score of 0 or 1 on the modified Rankin scale, a causative occlusion of the intracranial internal carotid artery or the first segment of the middle cerebral artery, an NIHSS score of 6 or higher, and an ASPECTS value of 6 or higher, in whom treatment was initiated (groin puncture) within 6 hours after onset.[5] MRA or CTA is necessary to show intracranial large-vessel occlusion. Two randomized, controlled trials that used only these neuroimaging methods showed a benefit of mechanical thrombectomy.[14,15] Although other trials used diffusion-weighted MRI, perfusion MRI, or perfusion CT to determine eligibility, such testing is not required and could lead to the exclusion of patients who might benefit from treatment.

Pooled data from five randomized, controlled trials showed that the percentage of patients who had a modified Rankin scale score of 0 to 2 at 90 days was higher among those who underwent stent-retriever mechanical thrombectomy than among those who did not (46.0% vs. 26.5%; adjusted odds ratio, 2.49; 95% CI, 1.76 to 3.53).[16] In both groups, 85% of the patients received

intravenous alteplase. Mechanical thrombectomy can also be performed alone in patients who are ineligible for intravenous alteplase because of the risk of bleeding. As with alteplase, the benefit of mechanical thrombectomy is time-dependent.[17]

These trials included few patients who had a causative occlusion of an intracranial artery other than the internal carotid artery or the first segment of the middle cerebral artery, a pre-stroke score of more than 1 on the modified Rankin scale, an ASPECTS value of lower than 6, or an NIHSS score of lower than 6; therefore, the benefits of mechanical thrombectomy are uncertain for these patients, but the procedure may be reasonable if performed within 6 hours after onset. Direct aspiration as a first approach for thrombectomy has been shown to be noninferior to stent retrievers.[18] Mechanical thrombectomy should be performed by qualified neurointerventionalists with comprehensive periprocedural care teams in specialized centers where cerebral angiography can be performed rapidly.

A randomized, controlled noninferiority trial that compared mechanical thrombectomy alone with the combination of intravenous alteplase and mechanical thrombectomy in patients eligible for both interventions met its large prespecified noninferiority margin (the modified Rankin scale score with thrombectomy alone at 90 days was less than 20% worse than that with combined therapy); the adjusted odds ratio was 1.07 (95% CI, 0.81 to 1.40).[19] This trial was carried out at centers where mechanical thrombectomy is performed, and the median delay from starting treatment with alteplase to groin puncture was 30 minutes; thus, the trial did not address the common scenario of initiating alteplase treatment locally, followed by transfer to another site for thrombectomy. Furthermore, all the participants had CTA documentation of intracranial large-vessel occlusion at randomization, whereas alteplase is often administered before CTA is performed. Current guidelines recommend that patients who are eligible for alteplase receive it even if mechanical thrombectomy is still under consideration.[5] It is prudent to continue this practice until further data are available.

Mechanical Thrombectomy at More Than 6 Hours after Stroke Onset

Two randomized, controlled trials have shown a benefit of mechanical thrombectomy performed at more than 6 hours after the onset of stroke in patients with an occlusion of the intracranial internal carotid artery or the first segment of the middle cerebral artery. The DAWN (Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention with Trevo) trial used the combination of an NIHSS score of 10 or higher and findings on perfusion CT or diffusion-weighted MRI with perfusion MRI to select patients who had an onset of stroke 6 to 24 hours earlier.[8] The percentage of patients with a score of 0 to 2 on the modified Rankin scale at 90 days was significantly higher among those who underwent mechanical thrombectomy than among those who did not (49% vs. 13%; adjusted difference, 33%; 95% CI, 21 to 44). The DEFUSE (Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution) 3 trial included patients who had an onset of stroke 6 to 16 hours earlier and had a large mismatch between the volume of the core and the volume of the penumbra and a maximum core size as determined by means of perfusion CT or diffusion-weighted MRI with perfusion MRI and an NIHSS score of 6 or higher.[9] The percentage of patients with a score of 0 to 2 on the modified Rankin scale at 90 days was significantly higher among those who underwent mechanical thrombectomy than among those who did not (45% vs. 17%; relative risk, 2.67; 95% CI, 1.60 to 4.48).

There are limited data to guide blood-pressure management in patients who undergo mechanical thrombectomy. Most patients who were enrolled in randomized, controlled trials within 6 hours after the onset of stroke received intravenous alteplase. The protocols of those trials stipulated that a blood pressure of 180/105 or lower be maintained in the patient during mechanical thrombectomy and for 24 hours after the procedure, and most of the trials excluded patients who had a blood pressure of higher than 185/110 mm Hg. The most appropriate blood-pressure management in patients not receiving alteplase is not known, but it is reasonable to maintain a blood pressure of 180/105 mm Hg or lower during the procedure and for 24 hours after the procedure.[5]

Tenecteplase

Tenecteplase is a tissue plasminogen activator that is modified to be more fibrin-specific and

more resistant to plasminogen activator inhibitor and to have a longer plasma half-life than alteplase so that it can be given as a single intravenous bolus. A meta-analysis of five randomized, controlled trials that compared tenecteplase with standard-dose alteplase for the treatment of acute ischemic stroke showed no significant difference between the two agents with respect to the percentage of patients who had a score of 0 or 1 on the modified Rankin scale at 90 days (58.2% vs. 55.6%; odds ratio, 1.17; 95% CI, 0.95 to 1.44).[20] Conclusions regarding the relative efficacy of tenecteplase are limited owing to the absence of a rigorous, generalizable, head-to-head trial with a primary clinical end point, heterogeneity among the trials with respect to the characteristics of the enrolled patients and the tenecteplase doses, the inclusion of multiple outcomes leading to an increased risk of type I error, and wide confidence intervals in the individual trials.

Antithrombotic Agents

In patients who receive intravenous alteplase, administration of an antiplatelet agent is generally delayed for 24 hours to minimize the risk of bleeding.[5] Pooled data from two large, randomized, placebo-controlled trials showed that the risk of recurrent stroke or death in the hospital was lower with aspirin (at a dose of 160 to 300 mg administered within 48 hours after acute ischemic stroke) than with placebo (8.2% vs. 9.1%, P=0.001).[21] In patients with an NIHSS score of 3 or lower who have no indication for long-term anticoagulation, the percentage of those who had a subsequent stroke (ischemic or hemorrhagic) over 90 days was lower with a 21-day course of dual antiplatelet treatment begun within 24 hours (clopidogrel at an initial dose of 300 mg, then 75 mg per day, plus aspirin at an initial dose of 75 to 300 mg, then 75 mg daily) followed by a course of clopidogrel (75 mg daily) than with aspirin alone (8.2% vs. 11.7%; hazard ratio, 0.69; 95% CI, 0.56 to 0.84).[22] This difference was maintained at 1 year (10.6% vs. 14.0%; hazard ratio, 0.78; 95% CI, 0.65 to 0.93).[23]

In a meta-analysis of randomized, controlled trials involving patients with acute ischemic stroke, the risk of death or disability at follow-up with therapeutic anticoagulation within 48 hours after onset was not lower than with aspirin or placebo.[24] Among a subgroup of patients with atrial fibrillation, the risk of recurrent ischemic stroke during the treatment period was significantly lower with therapeutic subcutaneous heparin (begun within 48 hours after onset and continued for 14 days) than with no heparin (2.3% vs. 4.9%); however, the risk of symptomatic intracerebral hemorrhage was higher with therapeutic subcutaneous heparin (2.8% vs. 0.4%), and the risk of death or disability at 6 months was not lower than with no heparin.[25]

General Medical and Supportive Care

Guidelines for general medical and supportive care are provided in Table 1. An algorithm for initial management of acute ischemic stroke is provided in Figure 2.

AREAS OF UNCERTAINTY

Comparative data regarding outcomes and cost-effectiveness are needed to improve systems of care before and during hospitalization, including the use of mobile stroke units — ambulances equipped with CT scanners, in which onboard physicians or physicians available by telemedicine can use CT results to make decisions about intravenous thrombolysis or transport.[26] Other uncertainties include the efficacy of mechanical thrombectomy within 6 hours after the onset of stroke in patients who have a causative occlusion of an intracranial artery other than the internal carotid artery or the first segment of the middle cerebral artery, a pre-stroke score of more than 1 on the modified Rankin scale, an ASPECTS value of lower than 6, or an NIHSS score of lower than 6; appropriate imaging criteria to select patients for an extended treatment window for intravenous alteplase (4.5 to 9.0 hours after the onset of stroke); the role of tenecteplase; blood-pressure targets before, during, and after mechanical thrombectomy for those who did not receive alteplase; and management of blood pressure of 220/120 mm Hg or higher in those who did not receive alteplase or mechanical thrombectomy.

GUIDELINES

Guidelines for the management of acute ischemic stroke have been published by professional organizations in the United States, Europe, Canada, and the United Kingdom.[5,27-30] All the guide-

Table 1. General Medical and Supportive Care for Patients with Acute Ischemic Stroke.*

Patients should be admitted to a specialized stroke unit.
Cardiac monitoring should be performed for at least the first 24 hours.
Supplemental oxygen should be provided to maintain oxygen saturation of higher than 94%, if necessary.
Sources of fever (temperature >38°C) should be identified and treated. Antipyretic medications should be administered to lower temperature in patients with hyperthermia.
Hyperglycemia should be treated to attain blood glucose levels in a range of 140 to 180 mg per deciliter, and treatment should be monitored closely to prevent hypoglycemia.
For patients with a blood pressure of lower than 220/120 mm Hg who did not receive intravenous alteplase or undergo mechanical thrombectomy and who do not have a coexisting medical complication that requires urgent antihypertensive treatment, treatment of hypertension within the first 48 to 72 hours after the onset of stroke does not reduce the risk of death or disability.
For patients with a blood pressure of 220/120 mm Hg or higher who did not receive intravenous alteplase or undergo mechanical thrombectomy and who do not have a coexisting medical complication that requires urgent antihypertensive treatment, the benefit of treating hypertension within the first 48 to 72 hours after the onset of stroke is uncertain. It may be reasonable to lower the blood pressure by 15% during the first 24 hours after the onset.
In immobile patients without contraindications, intermittent pneumatic compression stockings are recommended to reduce the risk of deep-vein thrombosis.
Screening for dysphagia can identify patients at increased risk for aspiration.
Patients with large cerebral and cerebellar infarctions are at high risk for brain swelling and herniation during the first days. These patients should be monitored closely. Neurosurgical intervention can be lifesaving in those with early decreased consciousness. If management of malignant brain swelling is unavailable locally, patients at risk for this condition should be transferred to an institution with expertise in such management.

* These guidelines were derived from the 2019 update to the 2018 American Heart Association/American Stroke Association guidelines for the early management of acute ischemic stroke.[5]

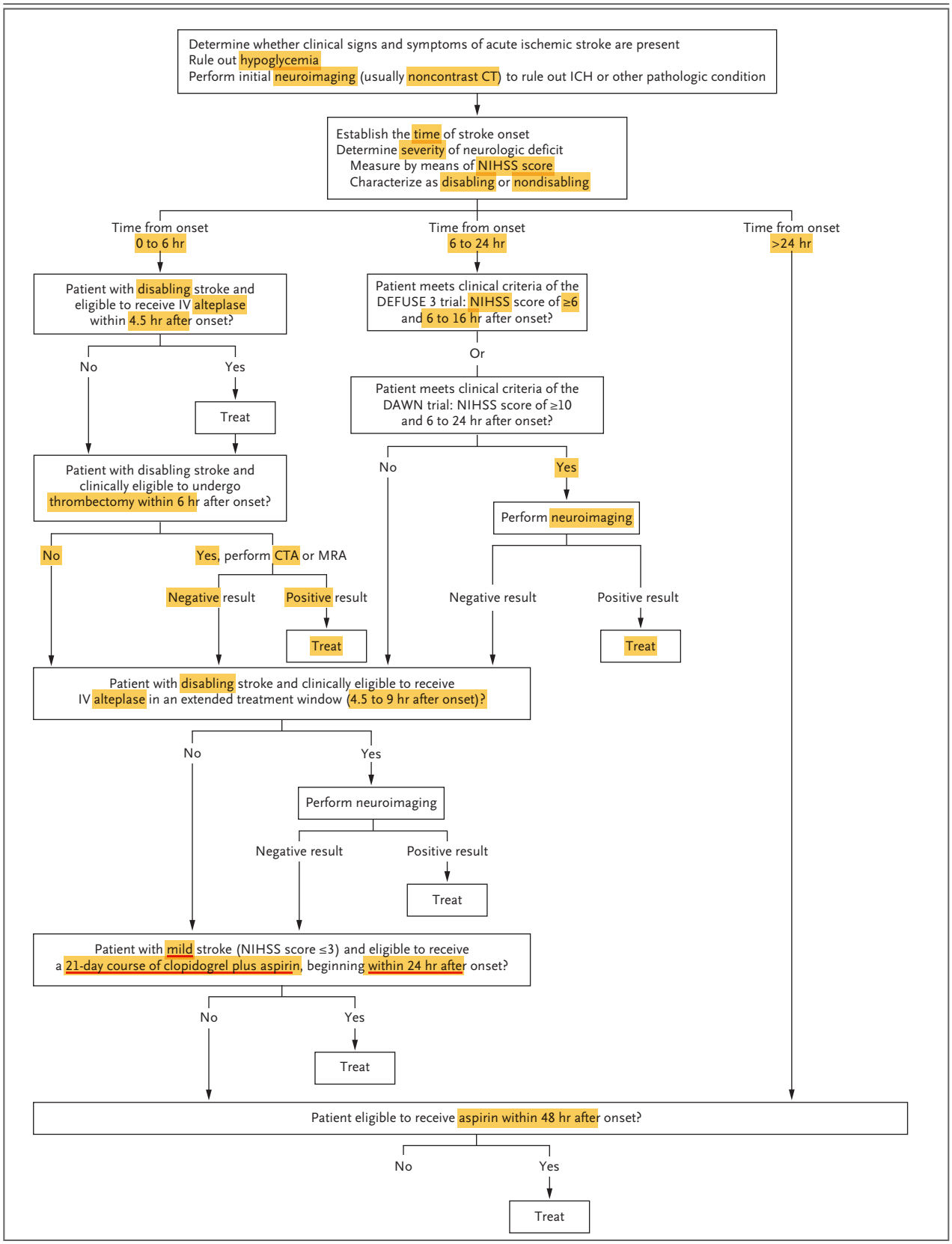
lines recommend intravenous alteplase within 4.5 hours after the onset of stroke and mechanical thrombectomy within 24 hours after onset in patients who meet criteria consistent with those in the aforementioned randomized trials. The recommendations presented here are consistent with those guidelines.

CONCLUSIONS AND RECOMMENDATIONS

The patient in the vignette has a disabling acute ischemic stroke in the territory of the left middle cerebral artery. Because the patient is within the 4.5-hour treatment window for standard intravenous alteplase and has no contraindications, he should receive intravenous alteplase immediately. CTA or MRA should be performed. If this cannot be done on site, the patient should be rapidly transferred to a hospital with resources to perform mechanical thrombectomy. If the patient has an occlusion of the internal carotid artery or the first segment of the middle cerebral artery, he should proceed immediately to undergo mechanical thrombectomy. Because the patient is within the 6-hour treatment window, no further neuroimaging is necessary. If there is a proximal occlusion in one of the main arterial branches off the first segment of the middle cerebral artery, thrombectomy may be reasonable because of the disabling nature of his deficit. The blood pressure should be maintained below 180/105 mm Hg. The patient should be admitted to an intensive care unit or specialized stroke unit for close neurologic monitoring and blood-pressure control if needed.

Figure 2 (facing page). Stepwise Algorithm for Initial Management of Acute Ischemic Stroke in Adults.

All inclusion and exclusion criteria for the specific therapeutic indication should be verified before treatment is instituted. By convention, the time of stroke onset is established as the time that the patient was last known to be well (i.e., in a normal or baseline state, as confirmed by medical history). CT denotes computed tomography, CTA computed tomography angiography, DAWN Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention with Trevo, DEFUSE Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution, ICH intracerebral hemorrhage, IV intravenous, MRA magnetic resonance angiography, and NIHSS National Institutes of Health Stroke Scale.



No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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