Approach to reperfusion therapy for acute ischemic stroke

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All topics are updated as new evidence becomes available and our peer review process is complete.
Literature review current through: Feb 2018. | **This topic last updated:** Mar 12, 2018.

INTRODUCTION — The most important factor in successful reperfusion therapy of acute ischemic stroke is early treatment. Nonetheless, selection of appropriate candidates for reperfusion demands a neurologic evaluation and a neuroimaging study. In addition, reperfusion therapy for acute stroke requires a system that coordinates emergency services, stroke neurology, intensive care services, neuroimaging, and neurosurgery to provide optimal treatment.

This topic will review the use of reperfusion therapy for patients with acute ischemic stroke, focusing on early thrombolytic therapy with intravenous alteplase. The administration of intravenous alteplase for acute ischemic stroke is reviewed in detail separately. (See "Intravenous thrombolytic therapy for acute ischemic stroke: Therapeutic use".)

Mechanical thrombectomy is reviewed in detail elsewhere. (See "Mechanical thrombectomy for acute ischemic stroke".)

TREATMENT OPTIONS — The immediate goal of reperfusion therapy for acute ischemic stroke is to restore blood flow to the regions of brain that are ischemic but not yet infarcted. The long-term goal is to improve outcome by reducing stroke-related disability and mortality.

There are two options for reperfusion therapy that are proven effective: intravenous alteplase and mechanical thrombectomy.

Alteplase — Intravenous alteplase (recombinant tissue plasminogen activator or tPA) is the mainstay of treatment for acute ischemic stroke, provided that treatment is initiated within 4.5 hours of clearly defined symptom onset (table 1). Because the benefit of alteplase is time dependent, it is critical to treat patients as quickly as possible. Alteplase initiates local fibrinolysis by binding to fibrin in a thrombus (clot) and converting entrapped plasminogen to plasmin. In turn, plasmin breaks up the thrombus into fibrin degradation products.

Benefit — Intravenous thrombolytic therapy with alteplase improves functional outcome at three to six months when given within 4.5 hours of ischemic stroke onset [1-7].

The benefit of intravenous thrombolysis for acute ischemic stroke decreases continuously over time from symptom onset, as shown in meta-analyses of randomized trials [1,3,4] and a registry that analyzed data from over 58,000 patients treated with tPA within 4.5 hours of ischemic stroke symptom onset [2]. In the registry, each 15-minute reduction in the time to initiation of tPA treatment was associated with an **increase** in the odds of walking independently at discharge (4 percent) and

being discharged to home rather than an institution (3 percent); in addition, the same 15-minute reduction in time to tPA treatment was associated with a **decrease** in the odds of death before discharge (4 percent) and symptomatic hemorrhagic transformation of infarction (4 percent) [2].

A 2014 meta-analysis evaluated individual patient data from 6756 subjects (including more than 1700 subjects older than age 80 years) who were allocated to intravenous alteplase or control within 3 to 6 hours of acute ischemic stroke onset in the NINDS, ATLANTIS, ECASS (1, 2, and 3), EPITHET, and IST-3 trials [4]. The primary outcome measure was the proportion of patients achieving a good stroke outcome at three or six months as defined by a modified Rankin scale score (table 2) of 0 or 1 (ie, no significant disability). The following observations were reported:

- For treatment within 3 hours of stroke onset, alteplase led to a good outcome for 33 percent, versus 23 percent for control (odds ratio [OR] 1.75, 95% CI 1.35-2.27). The number needed to treat (NNT) for one additional patient to achieve a good outcome was 10.
- For treatment from 3 to 4.5 hours, the proportion with a good outcome in the alteplase and control groups was 35 and 30 percent (OR 1.26, 95% CI 1.05-1.51, NNT 20).
- For treatment beyond 4.5 hours, the proportion with a good outcome in the alteplase and control groups was 33 and 31 percent (OR 1.15, 95% CI 0.95-1.40, NNT 50).
- The benefit of alteplase was similar regardless of patient age or stroke severity.
- Alteplase increased the risk of symptomatic intracranial hemorrhage (6.8 percent, versus 1.3 percent for control, OR 5.55, 95% CI 4.01-7.70); the number needed to harm (NNH) for one additional patient to have a symptomatic intracranial hemorrhage was 18.2. Alteplase also increased the risk of fatal intracranial hemorrhage within seven days (2.7 versus 0.4 percent, OR 7.14, 95% CI 3.98-12.79, NNH 44); this risk was similar regardless of age, stroke severity, or treatment delay. Alteplase treatment had no significant effect on other early or late causes of death.
- Death at 90 days was slightly higher in the alteplase group (17.9 percent, versus 16.5 percent in the control group, hazard ratio 1.11, 95% CI 0.99-1.25), a result that just missed statistical significance.

In agreement with other meta-analyses [1,3,7], these observations confirm that the sooner intravenous alteplase treatment is initiated, the more likely it is to be beneficial, and that the benefit extends to treatment started within 4.5 hours of stroke onset [4]. The results also show that alteplase is beneficial regardless of patient age, stroke severity, or the associated increased risk of symptomatic or fatal intracranial hemorrhage in the first days after alteplase treatment. The odds of a favorable three-month outcome decrease as the interval from stroke onset to start of alteplase treatment increases (figure 1) [1]. Beyond 4.5 hours, harm may exceed benefit.

Risk of intracerebral hemorrhage — Treatment with intravenous alteplase within 4.5 hours of acute ischemic stroke onset is associated with an increased early risk of intracerebral hemorrhage, but this risk is offset by later benefit in the form of reduced disability (see 'Benefit' above), and possibly by reduced mortality among those who do not have an intracerebral hemorrhage [6,8]. In clinical trials of intravenous alteplase, the rates of symptomatic intracerebral hemorrhage were 5 to 7 percent [4,9], using the National Institute of Neurological Disorders and Stroke (NINDS) definition. In addition, most community-based studies of intravenous alteplase have shown similar rates [10-14]. These studies suggest that intravenous alteplase can be used safely to treat acute ischemic stroke in routine clinical practice.

The NINDS trial definition of symptomatic intracerebral hemorrhage includes any hemorrhagic transformation temporally related to any neurologic worsening [9], which may be overly inclusive because it captures small petechial hemorrhages associated with minimal neurologic deterioration that are unlikely to have altered long-term functional outcome [15,16]. In contrast, the ECASS 2 and SITS-MOST definitions of symptomatic intracerebral hemorrhage includes only hemorrhage associated with substantial clinical worsening of ≥4 points on the NIHSS stroke scale [14], which may be more predictive of intracerebral hemorrhages that adversely affect long-term outcome. As an example, the SITS-MOST study enrolled over 30,000 patients, mainly from Europe, who were treated with intravenous alteplase at 669 centers [14]. Symptomatic intracerebral hemorrhage by the NINDS definition occurred in 7.4 percent, and by the SITS-MOST definition in 1.8 percent.

Several risk assessment methods, including the HAT score, DRAGON score, SEDAN score, Stroke-Thrombolytic Predictive Instrument, SPAN-100 index, and the SITS SICH risk score, have been devised to predict the risk of intracerebral hemorrhage and/or prognosis for patients with acute stroke who are treated with intravenous thrombolysis [14,17-25]. However, additional validation studies are needed to confirm the utility of these methods before they should be used in clinical practice.

Recanalization — Full or partial recanalization up to 24 hours after onset of acute stroke is associated with a more favorable outcome than persistent occlusion after thrombolysis [26-29]. A number of factors may affect the response to thrombolytic therapy, including location of the occlusion in the arterial tree, availability of collateral blood supply, and clot-specific factors such as size, composition, and source.

- **Clot size and site** – The following observations have been made regarding the size and site of the thromboembolic clot [30-38]:
    - Larger clots are more resistant to thrombolysis [30].
    - More proximal sites of occlusion in the cerebrovascular arterial tree are more resistant to thrombolysis than more distal sites. As an example, internal carotid artery occlusions are more resistant than middle cerebral artery occlusions to intravenous tPA treatment. This may be due at least in part to the larger size of clots that lodge in larger vessels [39].
    - Clot occluding the cervical internal carotid artery may promote adjacent thrombosis extending to the intracranial internal carotid artery, resulting in a very long thrombus that is unlikely to be lysed by intravenous tPA alone.
    - In large vessels, in situ thromboses associated with atherosclerotic lesions may be more resistant to recanalization than fibrin rich embolic occlusions arising from the heart.
- **Clot age and composition** – The age and composition of thromboembolic material likely affects its response to thrombolytic therapy [40,41]. The ability to recanalize in experimental embolic stroke is related to the amount of red cells in the emboli and inversely related to the volume of emboli and to the fibrin content and density of the clots [42]. Thrombolytic drugs are unlikely to disrupt other types of embolic material, such as calcific plaque and fat.

Other variables affecting outcome — Early recanalization is probably the most important determinant of good outcome after thrombolysis, but a number of additional variables may impact neurologic outcome and the risk of intracerebral hemorrhage [43]. These include age, sex, stroke severity, and early ischemic change on CT or MRI. However, these factors do not necessarily predict which patients will or will not benefit from intravenous alteplase. The only factor known to independently alter response to intravenous tPA is **time to treatment**. (See 'Benefit' above.)

Whenever possible, the potential risks and benefits of thrombolysis should be discussed objectively with the patient and/or family prior to initiating treatment. (See 'Informed decision-making' below.)

- **Age** – Patients age 80 years or older appear to benefit from intravenous thrombolysis despite a higher mortality rate compared with younger patients. (See 'Age 80 years and older' below.)

- **Stroke severity** – The severity of neurologic deficit as measured on the National Institutes of Health Stroke Scale (NIHSS) score (table 3) is associated with an increased risk of intracerebral hemorrhage [6,8]. However, stroke severity alone cannot be used to select or exclude patients for intravenous thrombolysis. A 2014 meta-analysis of individual patient data from 6756 subjects found that benefit of alteplase was similar regardless of stroke severity [4].

- **Early ischemic changes on CT** – The presence of extensive regions of obvious hypodensity consistent with irreversible injury on initial head CT is an exclusion for use of intravenous thrombolysis (table 1), as discussed below. (See 'Early ischemic changes on neuroimaging' below.)

- **Hyperglycemia** – Hyperglycemia before reperfusion in patients with acute ischemic stroke has been associated with diminished neurologic improvement, greater infarct size, and worse clinical outcome at three months after treatment with intravenous tPA [44-46].

- **Cerebral microbleeds** – Cerebral microbleeds are small chronic hemorrhages that are best visualized on susceptibility-weighted MRI sequences. (See "Spontaneous intracerebral hemorrhage: Pathogenesis, clinical features, and diagnosis", section on 'Microbleeds'.)

  Meta-analyses published in 2015 [47], 2016 [48], and 2017 [49] found that the presence of cerebral microbleeds on pretreatment brain MRI was associated with an increased risk of intracerebral hemorrhage (ICH) in patients treated with intravenous thrombolysis for acute ischemic stroke. In one of these reports, the risk of symptomatic ICH was significantly greater for patients with a high burden of cerebral microbleeds (>10) compared with patients who had a lower burden of microbleeds (1 to 10 or 0 to 10) [48]. However, the small number of patients in the subgroup with >10 microbleeds (n = 15) limits the strength of this conclusion. In another meta-analysis, the presence of cerebral microbleeds was not associated with symptomatic ICH but was associated with an increased risk of parenchymal hemorrhage, and the presence of >5 cerebral microbleeds was associated with poor functional outcome at three to six months [49].

- **Sex** – There are conflicting data regarding whether benefit from early intravenous thrombolysis of acute ischemic stroke differs by sex [50-52].

Mechanical thrombectomy — Endovascular treatment with mechanical thrombectomy using second-generation stent retriever devices improves outcomes for patients with acute ischemic stroke caused by an intracranial large artery occlusion in the proximal anterior circulation who can be treated within 6 hours of symptom onset, regardless of whether they receive intravenous alteplase for the same ischemic stroke event. (See "Mechanical thrombectomy for acute ischemic stroke".)

Eligible patients should receive intravenous alteplase without delay even if mechanical thrombectomy is being considered [53].

RAPID EVALUATION — All adult patients with a clinical diagnosis of acute ischemic stroke should be rapidly screened for treatment with intravenous thrombolytic therapy. Simultaneously, patients with suspected acute ischemic stroke involving the anterior circulation should be evaluated for mechanical thrombectomy.

In-hospital timeline — A door-to-needle time of ≤60 minutes is the benchmark for achieving rapid treatment with intravenous alteplase [53]. The following in-hospital timeline is suggested as a goal for all patients with acute ischemic stroke who are eligible for treatment with intravenous alteplase:

- Evaluation by physician – 10 minutes elapsed from arrival
- Stroke or neurologic expertise contacted (ie, stroke team) – ≤15 minutes elapsed
- Head CT or MRI scan – ≤25 minutes elapsed
- Interpretation of neuroimaging scan – ≤45 minutes elapsed
- Start of intravenous alteplase treatment – ≤60 minutes elapsed

Although intravenous alteplase treatment is the first priority, evaluation and preparation for possible mechanical thrombectomy should proceed during and after alteplase treatment. Patients with suspected infarction involving the anterior circulation should have cerebral angiography (eg, CT angiography or MR angiography) as soon as possible to determine whether they have a proximal intracranial large artery occlusion that might also benefit from mechanical thrombectomy. However, intravenous alteplase treatment should not be delayed by angiography or mechanical thrombectomy.

The administration of intravenous alteplase for acute ischemic stroke is reviewed in detail separately. (See "Intravenous thrombolytic therapy for acute ischemic stroke: Therapeutic use".)

Investigations — Diagnostic neuroimaging is essential before considering reperfusion therapy for acute ischemic stroke. In most cases, however, the results of routine laboratory tests including coagulation parameters and platelet count are not required to proceed with intravenous alteplase treatment. The only test that is mandatory for all patients before initiation of intravenous alteplase is blood glucose. Thrombolytic therapy with alteplase should not be delayed while results are pending unless one of the following conditions is present [53]:

- Clinical suspicion of a bleeding abnormality or thrombocytopenia
- Current or recent use of anticoagulants (eg, heparin, warfarin, direct oral anticoagulants)
- Use of anticoagulants is not known

For patients without recent use of oral anticoagulants or heparin, treatment with intravenous alteplase can be started before availability of coagulation test results. In such cases, treatment should be discontinued if the international normalized ratio (INR), prothrombin time (PT), or activated partial thromboplastin time (aPTT) are excessively elevated (table 1). For patients with inadequate historical information, alteplase therapy should not be started until the aPTT and either the PT or the INR are available.

Preliminary data suggest that normal coagulation parameters can be predicted on arrival to the emergency department by assessing three questions [54]:

- Is the patient taking an oral anticoagulant?
- Is the patient taking heparin or low molecular weight heparin?
- Is the patient on hemodialysis?

In a retrospective study from 2006 (prior to the advent of direct oral anticoagulants) that included 299 patients, "no" answers to all three questions predicted normal range PT and aPTT with a sensitivity of 100 percent, suggesting that this simple screen may permit earlier treatment with alteplase in

selected patients with acute stroke [54]. Other data suggest that unsuspected coagulopathy is rarely detected among patients evaluated for intravenous thrombolysis [55].

Potential exclusions to treatment — A number of clinical issues may complicate the decision to use reperfusion therapy for acute ischemic stroke. Among these are rapidly improving stroke symptoms and early ischemic changes on neuroimaging.

Rapidly improving stroke symptoms — Rapidly improving stroke symptoms (RISS) should be considered an exclusion for reperfusion therapy **only** for patients who improve to the degree that any remaining deficits are nondisabling [56]. The decision regarding use of intravenous alteplase or mechanical thrombectomy should be made based upon monitoring neurologic deficits for no longer than the time needed to prepare and begin treatment; treatment should not be delayed by continued monitoring for improvement.

Disabling stroke deficits — Qualifying patients who have an acute ischemic stroke causing a persistent neurologic deficit that is potentially disabling, despite improvement of any degree while being evaluated, should be treated urgently with intravenous alteplase and/or mechanical thrombectomy as appropriate. Any of the following should be considered disabling deficits [56]:

- Complete hemianopia: ≥2 on the National Institutes of Health Stroke Scale (NIHSS) question 3 (table 3)
- Severe aphasia: ≥2 on NIHSS question 9 (table 3)
- Visual or sensory extinction: ≥1 on NIHSS question 11 (table 3)
- Any weakness limiting sustained effort against gravity: ≥2 on NIHSS question 5 or 6 (table 3)
- Any deficits that lead to a total NIHSS >5 (calculator 1)
- Any remaining deficit considered potentially disabling by the patient, family, or the treating practitioner

Early ischemic changes on neuroimaging — Minor ischemic changes (ie, early signs of infarction) on CT are not a contraindication to treatment; these include subtle or small areas of hypodensity, loss of gray-white distinction, obscuration of the lentiform nucleus, or the presence of a hyperdense artery sign.

We suggest withholding thrombolytic therapy with alteplase for patients with extensive regions of obvious hypodensity consistent with irreversible injury on initial head CT (table 1), although there are few data to determine a threshold of ischemic severity or extent that modifies treatment response to alteplase [57].

Patient selection for mechanical thrombectomy requires that the infarct core is small, with only limited signs of early ischemic change on neuroimaging, as determined by the Alberta Stroke Program Early CT Score (ASPECTS). This method described in detail separately. (See "Mechanical thrombectomy for acute ischemic stroke".)

Informed decision-making — Alteplase is an approved therapy for acute ischemic stroke because of substantial evidence of safety and efficacy; consent is not required to administer alteplase as an emergent therapy if patient or surrogate consent is not possible [53]. In such cases, the need for informed consent is outweighed by the need for urgent intervention, and the patient can be treated under the principle of presumption of consent.

Whether to proceed to thrombolysis in an individual patient should be based upon a brief discussion of the risks and benefits with the patient and family, if possible. However, neurologic deficits caused by acute stroke often preclude the ability of the patient to participate in the decision. In addition, the circumstances of emergency stroke care, including the time-dependent nature of the benefits of thrombolysis, are not conducive to the process of informed consent [58].

Patient characteristics that can be identified in the emergency department do not predict whether a patient will respond to alteplase [59,60]. Some patients will accept any risk, including an increased risk of intracranial bleeding, for an increased chance of avoiding severe permanent disability. Others are more risk averse and prefer to accept disability, especially if there is a chance of recovery over time.

Explaining risks and benefits — Procedures for informed decision-making and informed consent vary among different centers; we explain the risks and benefits of alteplase as follows:

"There is a treatment for your stroke called alteplase that must be given within 4.5 hours after the stroke started. It is a 'clot-buster' drug. Overall, it is estimated that alteplase treatment is 10 times more likely to help than to harm eligible patients when given within 3 hours of stroke onset [61]. The likelihood of benefit decreases with time, but treatment is still more likely to help than harm up to 4.5 hours after the stroke begins. Thus, the potential benefits of this treatment outweigh the risks. However, this treatment has a major risk, since it can cause severe bleeding in the brain in about 1 of every 15 patients. If bleeding occurs in the brain, it can be fatal. When used to treat large numbers of stroke patients, on average the potential benefits of this treatment outweigh the risks; however, in any individual patient it is a very personal decision."

Need for transfer to stroke center — Most hospitals in the developed world are able to treat acute ischemic stroke with intravenous alteplase. In situations where local stroke expertise is not routinely or immediately available, accumulating data suggest that intravenous alteplase treatment can be performed safely and effectively via telemedicine (telestroke) [62].

In contrast, mechanical thrombectomy is not widely available. Transfer to an expert stroke center may be necessary for patients with acute ischemic stroke in the anterior circulation who present to medical facilities that lack resources and expertise to deliver mechanical thrombectomy. However, eligible patients can receive standard treatment with intravenous alteplase if they present to hospitals where thrombectomy is not an option, and those with qualifying anterior circulation strokes can then be transferred to tertiary stroke centers where intra-arterial thrombectomy is available, a strategy called "drip and ship" [63,64].

Reducing delay — Inordinate treatment delay can occur during any of the steps involved in reperfusion therapy, including initial telephone triage by the stroke physician, physician evaluation, neuroimaging, obtaining and waiting for results of blood and laboratory tests, obtaining consent, treating hypertension that would otherwise exclude the use of intravenous alteplase (tPA) (ie, systolic blood pressure ≥185 mmHg or diastolic ≥110 mmHg), and delivery of alteplase from the pharmacy to the bedside. Expedited stroke protocols may reduce treatment delays and improving patient outcomes. One such protocol includes the following features [65]:

- In-person triage of all code strokes without telephone triage; the stroke physician on-call proceeds immediately to the bedside
- Unmixed alteplase is available at the bedside during the evaluation
- No delays pending coagulation tests, chest x-ray, or stool guaiac unless specifically indicated

- No delays pending formal neuroimaging interpretation; the on-call stroke physician reads the brain CT or MRI scan
- No delays pending written consent; verbal consent is obtained if the patient is able to consent or if family members are nearby

TREATMENT BY TIME FROM SYMPTOM ONSET — "Time is brain." The sooner intravenous alteplase treatment is initiated after ischemic stroke, the more likely it is to be beneficial [66-68]. Eligible patients should be treated as quickly as possible within the appropriate 3 or 4.5 hour time limit; treatment should not be delayed until the end of the time window.

Mechanical thrombectomy is also time-dependent, with clear benefit for patients with acute ischemic stroke caused by an intracranial large artery occlusion in the proximal anterior circulation who are treated within 6 hours of symptom onset. Beyond 6 hours, mechanical thrombectomy may be an option at specialized stroke centers using imaging-based selection of patients with anterior circulation stroke who have symptom onset 6 to 24 hours before treatment. (See "Mechanical thrombectomy for acute ischemic stroke".)

Less than 3 hours — For eligible patients with acute ischemic stroke causing a potentially disabling neurologic deficit, we recommend intravenous alteplase therapy when treatment is initiated within 3 hours of clearly defined symptom onset. Patients in this time window should also be evaluated to determine if they are candidates for mechanical thrombectomy.

A meta-analysis of individual patient data from randomized controlled trials found that alteplase treatment within 3 hours of stroke onset led to a good outcome for 33 percent, versus 23 percent for control (odds ratio [OR] 1.75, 95% CI 1.35-2.27) [4].

3 to 4.5 hours — For otherwise eligible patients who cannot be treated in less than 3 hours, we suggest (ie, a weak recommendation) intravenous alteplase therapy provided that treatment is initiated within 3 to 4.5 hours of clearly defined symptom onset. Patients in this time window should also be evaluated to determine if they are candidates for mechanical thrombectomy.

The benefit of alteplase extends to 4.5 hours. A meta-analysis of individual patient data from randomized controlled trials found that alteplase treatment from 3 to 4.5 hours of stroke onset led to a good outcome for 35 percent, versus 30 percent for control (OR 1.26, 95% CI 1.05-1.51) [4].

There are additional exclusion criteria (table 1) for intravenous alteplase in the 3 to 4.5 hour time window (age >80 years old, an NIHSS score >25, a combination of previous stroke and diabetes, and oral anticoagulant use regardless of INR). However, we do not consider these as absolute contraindications to intravenous alteplase (tPA) treatment in the 3 to 4.5 hour time window, given evidence that alteplase is still beneficial in patients who would otherwise be excluded by these criteria [4,57,69,70]. The additional exclusions from 3 to 4.5 hours were made to satisfy safety concerns from the European regulatory agency and were employed to select patients for treatment in the ECASS 3 trial [71], which established the benefit of intravenous thrombolysis in the 3 to 4.5 hour time window.

4.5 to 6 hours — Patients within 4.5 to 6 hours from stroke symptom onset should **not** receive intravenous alteplase because harm may exceed benefit, but they should be evaluated to determine if they are candidates for mechanical thrombectomy. A meta-analysis of individual patient data from randomized controlled trials found that for treatment beyond 4.5 hours, the proportion with a good outcome in the alteplase and control groups was 33 and 31 percent (OR 1.15, 95% CI 0.95-1.40) [4].

6 to 24 hours — Patients beyond 6 hours from ischemic stroke symptom onset are not eligible for treatment with intravenous alteplase. However, mechanical thrombectomy is an option at specialized

stroke centers using imaging-based selection of patients with anterior circulation stroke who have were last known to be normal or at neurologic baseline 6 to 24 hours before treatment. This is discussed in detail separately. (See "Mechanical thrombectomy for acute ischemic stroke", section on 'Treatment beyond 6 hours'.)

Beyond 24 hours — Patients beyond 24 hours from ischemic stroke symptom onset are not eligible for treatment with intravenous alteplase or mechanical thrombectomy.

Unwitnessed stroke onset and "wake-up" stroke — When the exact time of stroke onset is not known, it is defined as the last time the patient was known to be normal. For patients whose stroke symptoms are first noted upon awakening from sleep, the last time known to be normal may be the time they went to bed (if the patient can report this reliably) or the last time seen normal by a friend or family member. Such patients are not eligible for alteplase treatment unless the time last known to be normal is less than 4.5 hours.

Limited evidence suggests that patients who wake up with ischemic stroke (ie, have an unknown time of stroke onset) and have no signs of early ischemic changes on neuroimaging can benefit from thrombolysis [72,73]. However, these findings require confirmation in randomized trials.

Imaging-based selection of patients for treatment with mechanical thrombectomy who were last known to be normal 6 to 24 hours before treatment is an option at specialized stroke centers. (See "Mechanical thrombectomy for acute ischemic stroke", section on 'Treatment beyond 6 hours'.)

SPECIAL POPULATIONS — Different clinical presentations and patient populations may affect the decision to use intravenous alteplase or mechanical thrombectomy for acute ischemic stroke, as discussed below.

Posterior circulation stroke — All eligible patients with acute ischemic stroke should be treated with intravenous alteplase, including those with stroke in the posterior circulation. Mechanical thrombectomy is beneficial for select patients with acute ischemic stroke caused by a proximal intracranial arterial occlusion in the anterior circulation, but trials that established the benefit of mechanical thrombectomy largely excluded patients with posterior circulation infarcts. However, endovascular interventions for vertebrobasilar occlusions, including mechanical thrombectomy, may be treatment options stroke centers with appropriate expertise. (See "Mechanical thrombectomy for acute ischemic stroke", section on 'Posterior circulation stroke'.)

Age 80 years and older — Patients age 80 years or older appear to benefit from intravenous thrombolysis despite a higher mortality rate compared with younger patients. Therefore, we do **not** consider age to be a contraindication to intravenous alteplase (tPA) treatment for otherwise eligible patients. However, age >80 years is a relative contraindication in the 3- to 4.5-hour time window. (See '3 to 4.5 hours' above.)

A 2014 meta-analysis of individual patient data from 6756 subjects (including more than 1700 subjects older than age 80 years) found that benefit of alteplase was similar regardless of patient age [4]. In a prespecified secondary analysis of individual participant data (n = 6756) from a 2016 meta-analysis of nine trials of alteplase versus control for acute ischemic stroke, the increased risk of intracerebral hemorrhage with alteplase in the first seven days after treatment did not differ by age [6].

Older age is not an exclusion for mechanical thrombectomy. (See "Mechanical thrombectomy for acute ischemic stroke", section on 'Patient selection'.)

Pregnancy — Although pregnancy has been considered a relative contraindication to the use of thrombolysis for acute stroke, intravenous alteplase can be given in pregnancy after careful

discussion of the potential risks and benefits. The use of thrombolytic therapy in pregnancy is discussed separately. (See "Cerebrovascular disorders complicating pregnancy", section on 'Acute reperfusion therapy'.)

Children — Safety and efficacy data for reperfusion therapy of acute ischemic stroke are lacking in patients younger than 18 years of age. However, intravenous alteplase and mechanical thrombectomy may be options for some children, particularly adolescents (age ≥13 years), with acute ischemic stroke on neuroimaging who are evaluated and treated at pediatric stroke centers. (See "Ischemic stroke in children: Evaluation, initial management, and prognosis", section on 'Thrombolysis and thrombectomy'.)

INVESTIGATIONAL THERAPIES — Investigational methods of reperfusion therapy for acute ischemic stroke include alternative fibrinolytic agents such as tenecteplase [74,75], intra-arterial infusion of thrombolytic agents such as alteplase, ultrasound-enhanced thrombolysis [76,77], combined intravenous and intra-arterial thrombolysis [78], and GP IIb/IIIa antagonists such as tirofiban [79-81].

However, these interventions remain unproven. For patients with acute ischemic stroke, the following treatments should not be used outside the setting of clinical trials [53]:

- Intravenous desmoteplase, urokinase, or any thrombolytic agents other than intravenous alteplase (tPA)
- Intravenous glycoprotein IIb/IIIa receptor inhibitors
- Combinations of interventions (other than intravenous alteplase and mechanical thrombectomy) to restore perfusion

SOCIETY GUIDELINE LINKS — Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Stroke in adults".)

SUMMARY AND RECOMMENDATIONS

- The immediate goal of reperfusion therapy for acute ischemic stroke is to restore blood flow to the regions of brain that are ischemic but not yet infarcted. Intravenous alteplase (tPA) is the mainstay of reperfusion therapy for acute ischemic stroke. Mechanical thrombectomy is indicated for patients with acute ischemic stroke caused by an intracranial large artery occlusion in the proximal anterior circulation. (See 'Treatment options' above.)
- Intravenous thrombolytic therapy with alteplase improves functional outcome at three to six months when given within 4.5 hours of ischemic stroke onset. (See 'Alteplase' above.)
- All adult patients with a clinical diagnosis of acute ischemic stroke should be rapidly screened for treatment with intravenous thrombolytic therapy. Simultaneously, patients with suspected acute ischemic stroke involving the anterior circulation should be evaluated for mechanical thrombectomy. (See 'Rapid evaluation' above.)
- For eligible patients (table 1) with acute ischemic stroke causing a potentially disabling neurologic deficit, we recommend intravenous alteplase therapy, provided that treatment is initiated within 3 hours of clearly defined symptom onset (**Grade 1A**). For otherwise eligible patients who cannot be treated in less than 3 hours, we suggest intravenous alteplase therapy, provided that treatment is initiated within 3 to 4.5 hours of clearly defined symptom onset (**Grade 2A**). (See 'Less than 3 hours' above and '3 to 4.5 hours' above.)

- Patients with acute ischemic stroke due to a proximal large artery occlusion who can be treated within 24 hours of time last known to be at neurologic baseline should be evaluated for treatment with mechanical thrombectomy. (See 'Treatment by time from symptom onset' above.)

REFERENCES

1. Lees KR, Bluhmki E, von Kummer R, et al. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. Lancet 2010; 375:1695.
2. Saver JL, Fonarow GC, Smith EE, et al. Time to treatment with intravenous tissue plasminogen activator and outcome from acute ischemic stroke. JAMA 2013; 309:2480.
3. Wardlaw JM, Murray V, Berge E, et al. Recombinant tissue plasminogen activator for acute ischaemic stroke: an updated systematic review and meta-analysis. Lancet 2012; 379:2364.
4. Emberson J, Lees KR, Lyden P, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. Lancet 2014; 384:1929.
5. Prabhakaran S, Ruff I, Bernstein RA. Acute stroke intervention: a systematic review. JAMA 2015; 313:1451.
6. Whiteley WN, Emberson J, Lees KR, et al. Risk of intracerebral haemorrhage with alteplase after acute ischaemic stroke: a secondary analysis of an individual patient data meta-analysis. Lancet Neurol 2016; 15:925.
7. Lees KR, Emberson J, Blackwell L, et al. Effects of Alteplase for Acute Stroke on the Distribution of Functional Outcomes: A Pooled Analysis of 9 Trials. Stroke 2016; 47:2373.
8. Whiteley WN, Slot KB, Fernandes P, et al. Risk factors for intracranial hemorrhage in acute ischemic stroke patients treated with recombinant tissue plasminogen activator: a systematic review and meta-analysis of 55 studies. Stroke 2012; 43:2904.
9. 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.
10. Albers GW, Bates VE, Clark WM, et al. Intravenous tissue-type plasminogen activator for treatment of acute stroke: the Standard Treatment with Alteplase to Reverse Stroke (STARS) study. JAMA 2000; 283:1145.
11. LaMonte MP, Bahouth MN, Magder LS, et al. A regional system of stroke care provides thrombolytic outcomes comparable with the NINDS stroke trial. Ann Emerg Med 2009; 54:319.
12. Hill MD, Buchan AM, Canadian Alteplase for Stroke Effectiveness Study (CASES) Investigators. Thrombolysis for acute ischemic stroke: results of the Canadian Alteplase for Stroke Effectiveness Study. CMAJ 2005; 172:1307.
13. Wahlgren N, Ahmed N, Dávalos A, et al. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. Lancet 2007; 369:275.
14. Mazya M, Egido JA, Ford GA, et al. Predicting the risk of symptomatic intracerebral hemorrhage in ischemic stroke treated with intravenous alteplase: safe Implementation of Treatments in Stroke (SITS) symptomatic intracerebral hemorrhage risk score. Stroke 2012; 43:1524.

15. Rao NM, Levine SR, Gornbein JA, Saver JL. Defining clinically relevant cerebral hemorrhage after thrombolytic therapy for stroke: analysis of the National Institute of Neurological Disorders and Stroke tissue-type plasminogen activator trials. Stroke 2014; 45:2728.
16. Gumbinger C, Gruschka P, Böttinger M, et al. Improved prediction of poor outcome after thrombolysis using conservative definitions of symptomatic hemorrhage. Stroke 2012; 43:240.
17. Lou M, Safdar A, Mehdiratta M, et al. The HAT Score: a simple grading scale for predicting hemorrhage after thrombolysis. Neurology 2008; 71:1417.
18. Strbian D, Meretoja A, Ahlhelm FJ, et al. Predicting outcome of IV thrombolysis-treated ischemic stroke patients: the DRAGON score. Neurology 2012; 78:427.
19. Kent DM, Selker HP, Ruthazer R, et al. The stroke-thrombolytic predictive instrument: a predictive instrument for intravenous thrombolysis in acute ischemic stroke. Stroke 2006; 37:2957.
20. McMeekin P, Flynn D, Ford GA, et al. Validating the stroke-thrombolytic predictive instrument in a population in the United kingdom. Stroke 2012; 43:3378.
21. Saposnik G, Guzik AK, Reeves M, et al. Stroke Prognostication using Age and NIH Stroke Scale: SPAN-100. Neurology 2013; 80:21.
22. Cucchiara B, Tanne D, Levine SR, et al. A risk score to predict intracranial hemorrhage after recombinant tissue plasminogen activator for acute ischemic stroke. J Stroke Cerebrovasc Dis 2008; 17:331.
23. Sung SF, Chen SC, Lin HJ, et al. Comparison of risk-scoring systems in predicting symptomatic intracerebral hemorrhage after intravenous thrombolysis. Stroke 2013; 44:1561.
24. Strbian D, Engelter S, Michel P, et al. Symptomatic intracranial hemorrhage after stroke thrombolysis: the SEDAN score. Ann Neurol 2012; 71:634.
25. Kent DM, Ruthazer R, Decker C, et al. Development and validation of a simplified Stroke-Thrombolytic Predictive Instrument. Neurology 2015; 85:942.
26. Neumann-Haefelin T, du Mesnil de Rochemont R, Fiebach JB, et al. Effect of incomplete (spontaneous and postthrombolytic) recanalization after middle cerebral artery occlusion: a magnetic resonance imaging study. Stroke 2004; 35:109.
27. Wunderlich MT, Goertler M, Postert T, et al. Recanalization after intravenous thrombolysis: does a recanalization time window exist? Neurology 2007; 68:1364.
28. Bhatia R, Hill MD, Shobha N, et al. Low rates of acute recanalization with intravenous recombinant tissue plasminogen activator in ischemic stroke: real-world experience and a call for action. Stroke 2010; 41:2254.
29. Kharitonova TV, Melo TP, Andersen G, et al. Importance of cerebral artery recanalization in patients with stroke with and without neurological improvement after intravenous thrombolysis. Stroke 2013; 44:2513.
30. Zivin JA, Fisher M, DeGirolami U, et al. Tissue plasminogen activator reduces neurological damage after cerebral embolism. Science 1985; 230:1289.
31. Mori E, Yoneda Y, Tabuchi M, et al. Intravenous recombinant tissue plasminogen activator in acute carotid artery territory stroke. Neurology 1992; 42:976.
32. Wolpert SM, Bruckmann H, Greenlee R, et al. Neuroradiologic evaluation of patients with acute stroke treated with recombinant tissue plasminogen activator. The rt-PA Acute Stroke Study Group. AJNR Am J Neuroradiol 1993; 14:3.

33. von Kummer R, Holle R, Rosin L, et al. Does arterial recanalization improve outcome in carotid territory stroke? Stroke 1995; 26:581.
34. Suarez JI, Sunshine JL, Tarr R, et al. Predictors of clinical improvement, angiographic recanalization, and intracranial hemorrhage after intra-arterial thrombolysis for acute ischemic stroke. Stroke 1999; 30:2094.
35. Linfante I, Llinas RH, Selim M, et al. Clinical and vascular outcome in internal carotid artery versus middle cerebral artery occlusions after intravenous tissue plasminogen activator. Stroke 2002; 33:2066.
36. Molina CA, Montaner J, Arenillas JF, et al. Differential pattern of tissue plasminogen activator-induced proximal middle cerebral artery recanalization among stroke subtypes. Stroke 2004; 35:486.
37. Lee KY, Han SW, Kim SH, et al. Early recanalization after intravenous administration of recombinant tissue plasminogen activator as assessed by pre- and post-thrombolytic angiography in acute ischemic stroke patients. Stroke 2007; 38:192.
38. Saqqur M, Uchino K, Demchuk AM, et al. Site of arterial occlusion identified by transcranial Doppler predicts the response to intravenous thrombolysis for stroke. Stroke 2007; 38:948.
39. Seners P, Turc G, Maïer B, et al. Incidence and Predictors of Early Recanalization After Intravenous Thrombolysis: A Systematic Review and Meta-Analysis. Stroke 2016; 47:2409.
40. Fulgham JR, Ingall TJ, Stead LG, et al. Management of acute ischemic stroke. Mayo Clin Proc 2004; 79:1459.
41. Kim EY, Heo JH, Lee SK, et al. Prediction of thrombolytic efficacy in acute ischemic stroke using thin-section noncontrast CT. Neurology 2006; 67:1846.
42. Overgaard K. Thrombolytic therapy in experimental embolic stroke. Cerebrovasc Brain Metab Rev 1994; 6:257.
43. Karaszewski B, Houlden H, Smith EE, et al. What causes intracerebral bleeding after thrombolysis for acute ischaemic stroke? Recent insights into mechanisms and potential biomarkers. J Neurol Neurosurg Psychiatry 2015; 86:1127.
44. Alvarez-Sabín J, Molina CA, Montaner J, et al. Effects of admission hyperglycemia on stroke outcome in reperfused tissue plasminogen activator--treated patients. Stroke 2003; 34:1235.
45. Ahmed N, Dávalos A, Eriksson N, et al. Association of admission blood glucose and outcome in patients treated with intravenous thrombolysis: results from the Safe Implementation of Treatments in Stroke International Stroke Thrombolysis Register (SITS-ISTR). Arch Neurol 2010; 67:1123.
46. Masrur S, Cox M, Bhatt DL, et al. Association of Acute and Chronic Hyperglycemia With Acute Ischemic Stroke Outcomes Post-Thrombolysis: Findings From Get With The Guidelines-Stroke. J Am Heart Assoc 2015; 4:e002193.
47. Charidimou A, Shoamanesh A, Wilson D, et al. Cerebral microbleeds and postthrombolysis intracerebral hemorrhage risk Updated meta-analysis. Neurology 2015; 85:927.
48. Tsivgoulis G, Zand R, Katsanos AH, et al. Risk of Symptomatic Intracerebral Hemorrhage After Intravenous Thrombolysis in Patients With Acute Ischemic Stroke and High Cerebral Microbleed Burden: A Meta-analysis. JAMA Neurol 2016; 73:675.
49. Charidimou A, Turc G, Oppenheim C, et al. Microbleeds, Cerebral Hemorrhage, and Functional Outcome After Stroke Thrombolysis: Individual Patient Data Meta-Analysis. Stroke 2017.

50. Kent DM, Price LL, Ringleb P, et al. Sex-based differences in response to recombinant tissue plasminogen activator in acute ischemic stroke: a pooled analysis of randomized clinical trials. Stroke 2005; 36:62.
51. Meseguer E, Mazighi M, Labreuche J, et al. Outcomes of intravenous recombinant tissue plasminogen activator therapy according to gender: a clinical registry study and systematic review. Stroke 2009; 40:2104.
52. Hametner C, MacIsaac RL, Kellert L, et al. Sex and Stroke in Thrombolyzed Patients and Controls. Stroke 2017; 48:367.
53. Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2018; 49:e46.
54. Gottesman RF, Alt J, Wityk RJ, Llinas RH. Predicting abnormal coagulation in ischemic stroke: reducing delay in rt-PA use. Neurology 2006; 67:1665.
55. Rost NS, Masrur S, Pervez MA, et al. Unsuspected coagulopathy rarely prevents IV thrombolysis in acute ischemic stroke. Neurology 2009; 73:1957.
56. Re-examining Acute Eligibility for Thrombolysis (TREAT) Task Force:, Levine SR, Khatri P, et al. Review, historical context, and clarifications of the NINDS rt-PA stroke trials exclusion criteria: Part 1: rapidly improving stroke symptoms. Stroke 2013; 44:2500.
57. Demaerschalk BM, Kleindorfer DO, Adeoye OM, et al. Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2016; 47:581.
58. Schwamm LH. Acute Stroke: Shifting From Informed Consent to Informed Refusal of Intravenous Tissue-Type Plasminogen Activator. Circ Cardiovasc Qual Outcomes 2015; 8:S69.
59. Generalized efficacy of t-PA for acute stroke. Subgroup analysis of the NINDS t-PA Stroke Trial. Stroke 1997; 28:2119.
60. Kasner SE, Grotta JC. Emergency identification and treatment of acute ischemic stroke. Ann Emerg Med 1997; 30:642.
61. Demaerschalk BM. Thrombolytic therapy for acute ischemic stroke: the likelihood of being helped versus harmed. Stroke 2007; 38:2215.
62. Kepplinger J, Barlinn K, Deckert S, et al. Safety and efficacy of thrombolysis in telestroke: A systematic review and meta-analysis. Neurology 2016; 87:1344.
63. Sheth KN, Smith EE, Grau-Sepulveda MV, et al. Drip and ship thrombolytic therapy for acute ischemic stroke: use, temporal trends, and outcomes. Stroke 2015; 46:732.
64. Deguchi I, Mizuno S, Kohyama S, et al. Drip-and-Ship Thrombolytic Therapy for Acute Ischemic Stroke. J Stroke Cerebrovasc Dis 2018; 27:61.
65. Sattin JA, Olson SE, Liu L, et al. An expedited code stroke protocol is feasible and safe. Stroke 2006; 37:2935.
66. Strbian D, Soinne L, Sairanen T, et al. Ultraearly thrombolysis in acute ischemic stroke is associated with better outcome and lower mortality. Stroke 2010; 41:712.
67. Ebinger M, Winter B, Wendt M, et al. Effect of the use of ambulance-based thrombolysis on time to thrombolysis in acute ischemic stroke: a randomized clinical trial. JAMA 2014; 311:1622.

68. Fonarow GC, Zhao X, Smith EE, et al. Door-to-needle times for tissue plasminogen activator administration and clinical outcomes in acute ischemic stroke before and after a quality improvement initiative. JAMA 2014; 311:1632.
69. Cronin CA, Shah N, Morovati T, et al. No increased risk of symptomatic intracerebral hemorrhage after thrombolysis in patients with European Cooperative Acute Stroke Study (ECASS) exclusion criteria. Stroke 2012; 43:1684.
70. Hill MD, Coutts SB. Alteplase in acute ischaemic stroke: the need for speed. Lancet 2014; 384:1904.
71. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med 2008; 359:1317.
72. Barreto AD, Martin-Schild S, Hallevi H, et al. Thrombolytic therapy for patients who wake-up with stroke. Stroke 2009; 40:827.
73. Manawadu D, Bodla S, Jarosz J, et al. A case-controlled comparison of thrombolysis outcomes between wake-up and known time of onset ischemic stroke patients. Stroke 2013; 44:2226.
74. Parsons M, Spratt N, Bivard A, et al. A randomized trial of tenecteplase versus alteplase for acute ischemic stroke. N Engl J Med 2012; 366:1099.
75. Logallo N, Novotny V, Assmus J, et al. Tenecteplase versus alteplase for management of acute ischaemic stroke (NOR-TEST): a phase 3, randomised, open-label, blinded endpoint trial. Lancet Neurol 2017; 16:781.
76. Ricci S, Dinia L, Del Sette M, et al. Sonothrombolysis for acute ischaemic stroke. Cochrane Database Syst Rev 2012; :CD008348.
77. Nacu A, Kvistad CE, Naess H, et al. NOR-SASS (Norwegian Sonothrombolysis in Acute Stroke Study): Randomized Controlled Contrast-Enhanced Sonothrombolysis in an Unselected Acute Ischemic Stroke Population. Stroke 2017; 48:335.
78. Broderick JP, Palesch YY, Demchuk AM, et al. Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. N Engl J Med 2013; 368:893.
79. Siebler M, Hennerici MG, Schneider D, et al. Safety of Tirofiban in acute Ischemic Stroke: the SaTIS trial. Stroke 2011; 42:2388.
80. Ciccone A, Motto C, Abraha I, et al. Glycoprotein IIb-IIIa inhibitors for acute ischaemic stroke. Cochrane Database Syst Rev 2014; :CD005208.
81. Li W, Lin L, Zhang M, et al. Safety and Preliminary Efficacy of Early Tirofiban Treatment After Alteplase in Acute Ischemic Stroke Patients. Stroke 2016; 47:2649.

Topic 115775 Version 2.0

GRAPHICS

Eligibility criteria for the treatment of acute ischemic stroke with intravenous alteplase (recombinant tissue plasminogen activator or tPA)

Inclusion criteria
Clinical diagnosis of ischemic stroke causing measurable neurologic deficit
Onset of symptoms <4.5 hours before beginning treatment; if the exact time of stroke onset is not known, it is defined as the last time the patient was known to be normal or at neurologic baseline
Age ≥18 years
Exclusion criteria
Historical
Ischemic stroke or severe head trauma in the previous three months
Previous intracranial hemorrhage
Intra-axial intracranial neoplasm
Gastrointestinal malignancy or hemorrhage in the previous 21 days
Intracranial or intraspinal surgery within the prior three months
Clinical
Symptoms suggestive of subarachnoid hemorrhage
Persistent blood pressure elevation (systolic ≥185 mmHg or diastolic ≥110 mmHg)
Active internal bleeding
Presentation consistent with infective endocarditis
Stroke known or suspected to be associated with aortic arch dissection
Acute bleeding diathesis, including but not limited to conditions defined in 'Hematologic'
Hematologic
Platelet count <100,000/mm^3*
Current anticoagulant use with an INR >1.7 or PT >15 seconds or aPTT >40 seconds or PT >15 seconds*
Therapeutic doses of low molecular weight heparin received within 24 hours (eg, to treat VTE and ACS); this exclusion does not apply to prophylactic doses (eg, to prevent VTE)
Current use of a direct thrombin inhibitor or direct factor Xa inhibitor with evidence of anticoagulant effect by laboratory tests such as aPTT, INR, ECT, TT, or appropriate factor Xa activity assays
Head CT scan
Evidence of hemorrhage
Extensive regions of obvious hypodensity consistent with irreversible injury
Relative exclusions/warnings ¶
Only minor and isolated neurologic signs or rapidly improving symptoms Δ
Serum glucose <50 mg/dL (<2.8 mmol/L) ◇
Serious trauma in the previous 14 days §
Major surgery in the previous 14 days ¥
History of gastrointestinal bleeding (remote) or genitourinary bleeding ‡
Seizure at the onset of stroke with postictal neurologic impairments †
Pregnancy**
Arterial puncture at a noncompressible site in the previous seven days ¶¶

Large (≥10 mm), untreated, unruptured intracranial aneurysm¶¶
Untreated intracranial vascular malformation¶¶
Additional relative exclusion criteria for treatment from 3 to 4.5 hours from symptom onsetΔΔ
Age >80 years
Oral anticoagulant use regardless of INR
Severe stroke (NIHSS score >25)
Combination of both previous ischemic stroke and diabetes mellitus

ACS: acute coronary syndrome; aPTT: activated partial thromboplastin time; ECT: ecarin clotting time; INR: international normalized ratio; PT: prothrombin time; NIHSS: National Institutes of Health Stroke Scale; tPA: intravenous alteplase; TT: thrombin time; VTE, venous thromboembolism.

* Although it is desirable to know the results of these tests, thrombolytic therapy should not be delayed while results are pending unless (1) there is clinical suspicion of a bleeding abnormality or thrombocytopenia, (2) the patient is currently on or has recently received anticoagulants (eg, heparin, warfarin, a direct thrombin inhibitor, or a direct factor Xa inhibitor), (3) use of anticoagulants is not known. For patients without recent use of oral anticoagulants or heparin, treatment with intravenous tPA can be started before availability of coagulation test results but should be discontinued if the INR, PT, or aPTT exceed the limits stated in the table.

¶ With careful consideration and weighting of risk-to-benefit, patients may receive intravenous alteplase despite one or more relative contraindications or warnings.

Δ Patients who have a persistent neurologic deficit that is potentially disabling, despite improvement of any degree, should be treated with tPA in the absence of other contraindications. Any of the following should be considered disabling deficits:

- Complete hemianopsia: ≥2 on NIHSS question 3, or
- Severe aphasia: ≥2 on NIHSS question 9, or
- Visual or sensory extinction: ≥1 on NIHSS question 11, or
- Any weakness limiting sustained effort against gravity: ≥2 on NIHSS question 5 or 6, or
- Any deficits that lead to a total NIHSS >5, or
- Any remaining deficit considered potentially disabling in the view of the patient and the treating practitioner using clinical judgment

◇ Patients may be treated with intravenous alteplase if glucose level is subsequently normalized.

§ The potential risks of bleeding with alteplase from injuries related to the trauma should be weighed against the anticipated benefits of reduced stroke-related neurologic deficits.

¥ The increased risk of surgical site bleeding with alteplase should be weighed against the anticipated benefits of reduced stroke-related neurologic deficits.

‡ There is a low increased risk of new bleeding with alteplase in the setting of past gastrointestinal or genitourinary bleeding. However, alteplase administration within 21 days of gastrointestinal bleeding is not recommended.

† Alteplase is reasonable in patients with a seizure at stroke onset if evidence suggests that residual impairments are secondary to acute ischemic stroke and not to a postictal phenomenon.

** Alteplase can be given in pregnancy when the anticipated benefits of treating moderate or severe stroke outweigh the anticipated increased risks of uterine bleeding.

¶¶ The safety and efficacy of administering alteplase is uncertain for these relative exclusions.

ΔΔ Intravenous alteplase appears to be safe and may be beneficial for patients with these relative exclusions, including patients taking oral anticoagulants with an INR <1.7.

Adapted from:

1. *Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med 2008; 359:1317.*
2. *Del Zoppo GJ, Saver JL, Jauch EC, et al. Expansion of the time window for treatment of acute ischemic stroke with intravenous tissue plasminogen activator. A science advisory from the American Heart Association/American Stroke Association. Stroke 2009; 40:2945.*
3. *Re-examining Acute Eligibility for Thrombolysis (TREAT) Task Force:, Levine SR, Khatri P, et al. Review, historical context, and clarifications of the NINDS rt-PA stroke trials exclusion criteria: Part 1: rapidly improving stroke symptoms. Stroke 2013; 44:2500.*
4. *Demaerschalk BM, Kleindorfer DO, Adeoye OM, et al. Scientific rationale for the inclusion and exclusion criteria for intravenous alteplase in acute ischemic stroke: A statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2016; 47:581.*
5. *Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 Guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2018; 49:e46.*

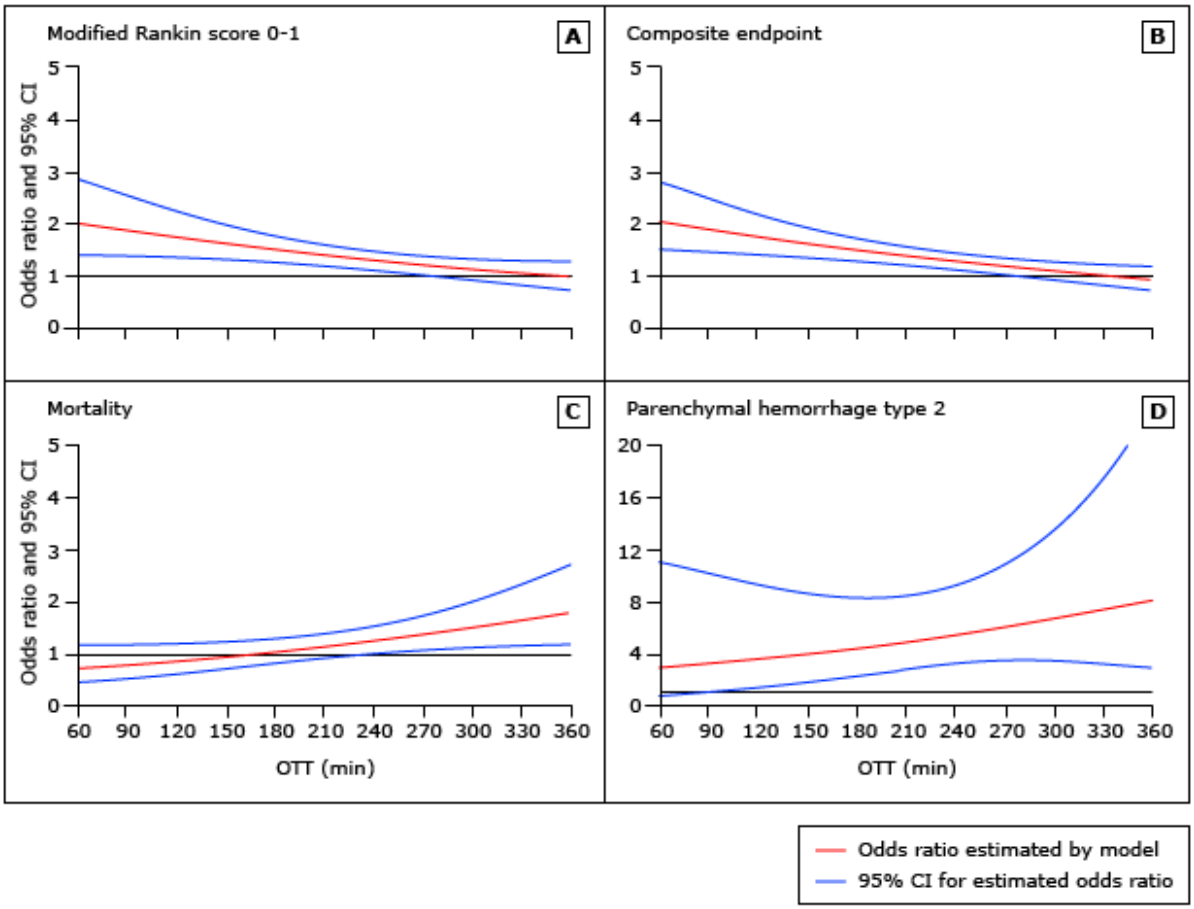
Graphic 71462 Version 19.0

Modified Rankin scale

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent, and requiring constant nursing care and attention
6	Dead

Graphic 75411 Version 12.0

Stroke treatment delay and outcome



Relation of stroke onset to start of treatment (OTT) with treatment effect after adjustment for prognostic variables assessed by A) day 90 modified Rankin score 0-1 versus 2-6 (interaction p=0.0269, n=3530 [excluding EPITHET data p=0.0116, n=3431]); B) global test that incorporates modified Rankin score 0-1 versus 2-6, Barthel Index score 95-100 versus 90 or lower and NIHSS score 0-1 versus 2 or more (interaction p=0.0111, n=3535 [excluding EPITHET data p=0.0049, n=3436]); C) mortality (interaction p=0.0444, n=3530 [excluding EPITHET data p=0.0582, n=3431]); and D) parenchymal hemorrhage type 2 (interaction p=0.4140, n=3531 [excluding EPITHET data p=0.4578, n=3431]). Thus, for parenchymal hemorrhage type 2, the fitted line is not statistically distinguishable from a horizontal line. For each graph, the adjusted odds ratio is shown with the 95% CIs. CIs from the models will differ from those shown in the tables because the model uses data from all patients treated within 0-360 min whereas the categorized analyses in the tables are based on subsets of patients: the modeled CIs are deemed to be more reliable.

%: percent.

Lees, KR, Bluhmki, E, von Kummer, R, et al. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. Lancet 2010; 375:1695. Illustration used with permission of Elsevier Inc. All rights reserved.

Graphic 66764 Version 2.0

National Institutes of Health Stroke Scale (NIHSS)

Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (ie, repeated requests to patient to make a special effort).

Instructions	Scale definition	Score
1a. Level of consciousness: The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = **Alert;** keenly responsive. 1 = **Not alert;** but arousable by minor stimulation to obey, answer, or respond. 2 = **Not alert;** requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic.	_____
1b. LOC questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.	0 = **Answers** both questions correctly. 1 = **Answers** one question correctly. 2 = **Answers** neither question correctly.	_____
1c. LOC commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (ie, follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	0 = **Performs** both tasks correctly. 1 = **Performs** one task correctly. 2 = **Performs** neither task correctly.	_____
2. Best gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be	0 = **Normal.** 1 = **Partial gaze palsy;** gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2 = **Forced deviation,** or total gaze paresis not overcome by the oculocephalic maneuver.	_____

tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.		
3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to respond to item 11.	0 = **No visual loss.** 1 = **Partial hemianopia.** 2 = **Complete hemianopia.** 3 = **Bilateral hemianopia** (blind including cortical blindness).	_____
4. Facial palsy: Ask - or use pantomime to encourage - the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.	0 = **Normal** symmetrical movements. 1 = **Minor paralysis** (flattened nasolabial fold, asymmetry on smiling). 2 = **Partial paralysis** (total or near-total paralysis of lower face). 3 = **Complete paralysis** of one or both sides (absence of facial movement in the upper and lower face).	_____
5. Motor arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift;** limb holds 90 (or 45) degrees for full 10 seconds. 1 = **Drift;** limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = **Some effort against gravity;** limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = **No effort against gravity;** limb falls. 4 = **No movement.** UN = **Amputation** or joint fusion, explain:_____ **5a. Left arm** **5b. Right arm**	_____
6. Motor leg: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift;** leg holds 30-degree position for full 5 seconds. 1 = **Drift;** leg falls by the end of the 5-second period but does not hit bed. 2 = **Some effort against gravity;** leg falls to bed by 5 seconds, but has some effort against gravity. 3 = **No effort against gravity;** leg falls to bed immediately. 4 = **No movement.** UN = **Amputation** or joint fusion, explain:_____	_____

	6a. Left leg **6b. Right leg**	
7. Limb ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.	0 = **Absent.** 1 = **Present in one limb.** 2 = **Present in two limbs.** UN = **Amputation** or joint fusion, explain:_____	_____
8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.	0 = **Normal;** no sensory loss. 1 = **Mild-to-moderate sensory loss;** patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched. 2 = **Severe to total sensory loss;** patient is not aware of being touched in the face, arm, and leg.	_____
9. Best language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.	0 = **No aphasia;** normal. 1 = **Mild-to-moderate aphasia;** some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. 2 = **Severe aphasia;** all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = **Mute, global aphasia;** no usable speech or auditory comprehension.	_____
10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of	0 = **Normal.** 1 = **Mild-to-moderate dysarthria;** patient slurs at least some words and, at worst, can be understood with some difficulty.	_____

articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.	2 = **Severe dysarthria;** patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. UN = **Intubated** or other physical barrier, explain:_____	
11. Extinction and inattention (formerly neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosognosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.	0 = **No abnormality.** 1 = **Visual, tactile, auditory, spatial, or personal inattention** or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = **Profound hemi-inattention or extinction to more than one modality;** does not recognize own hand or orients to only one side of space.	_____
		_____

Adapted from: Goldstein LB, Samsa GP, Stroke 1997; 28:307.

Graphic 61698 Version 4.0

Contributor Disclosures

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