



Clinical Practice Title: Initial Evaluation and Treatment of Patients presenting with Acute Ischemic Stroke or Transient Ischemic Attack, Including the Use of Thrombolytics	
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Brief Description of Clinical Practice			
All adult patients who present to the Emergency Department (ED) with acute neurologic symptoms consistent with stroke will undergo emergent evaluation and treatment, including high acuity assignment in triage, a standard focused history, a standard focused neurological exam, expedited diagnostics including continuous cardiac monitoring and a stat brain CT without contrast, and prompt control of blood pressure and blood glucose as indicated.			
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Initial Evaluation and Treatment of Patients presenting with Acute Ischemic Stroke or Transient Ischemic Attack, Including the Use of Thrombolytics

PRACTICE APPROACH:

Expected Clinical Practice

PRACTICE STATEMENT:

All adult patients who present to the Emergency Department (ED) with acute neurologic symptoms consistent with stroke will undergo emergent evaluation and treatment, including high acuity assignment in triage, a standard focused history, a standard focused neurological exam, expedited diagnostics including continuous cardiac monitoring and a stat brain CT without contrast, and prompt control of blood pressure and blood glucose as indicated.

All adult patients who present to the Emergency Department (ED) with an acute *ischemic* stroke will be evaluated as candidates for treatment with intravenous (IV) thrombolysis having meet specific criteria for the administration of IV thrombolytics.

Transient Ischemic Attack patients will be expeditiously evaluated and triaged in a manner similar to acute ischemic strokes. Depending on an assessment of risk, such patients will be managed in observation units, as inpatients and, at times, in specialized outpatient clinics with urgent access availability.

RATIONALE:

Stroke is the fourth leading cause of death in the United States, and the leading cause of adult disability in North America. Ischemic strokes account for 87% of the estimated 795,000 new strokes that occur in the U.S. each year.¹

The evaluation and treatment of patients presenting with an acute ischemic stroke is a critical priority in the Emergency Department.



Existing and evolving clinical evidence demonstrates that timely evaluation of potential stroke patients in the ED improves both short- and long-term clinical outcomes. Prompt identification of patients with an acute ischemic stroke facilitates effective delivery of time-sensitive therapies, including IV thrombolysis, which must be delivered within a narrow therapeutic window.

IV thrombolysis represents the only Class-I Level-A evidence-based treatment for providing emergent reperfusion of ischemic brain, yet evidence suggests that this intervention remains underused in the ED setting.

A Transient Ischemic Attack (TIA) is now defined as a transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia, without evidence of acute infarction.²

TIA's are common, occurring at an incidence estimated between 200,000 and 500,000 per year.³ Ten to 15% of TIA patients will have a stroke within 3 months, and half of those strokes will occur within 48 hours of the TIA.² Clinical trials show urgent evaluation and intervention in TIA patients can dramatically reduce this risk.⁴⁻⁶ Simple clinical grading scales can be applied to TIA patients to determine what setting of evaluation and treatment is appropriate: in observation units, as inpatients, or in specialized outpatient clinics with urgent appointment availability.

The principal rationale for this clinical practice is derived from current national guidelines for the early management of stroke and TIA, supplemented by the primary literature where indicated.

CLINICAL APPROACH:

The goal of the rapid assessment of all acute stroke-like symptoms is to complete the initial evaluation and initiate definitive management within 60 minutes of patient arrival in the ED.

Patients diagnosed with an acute ischemic stroke, who meet specific criteria for the administration of IV thrombolytics, will be administered IV-tPA.

I. TRIAGE

The narrow therapeutic window available for appropriate interventions in acute ischemic stroke requires an efficient and rapid pathway for evaluation, diagnosis, and treatment. Patients with stroke may clinically decline rapidly during the acute phase.

All patients presenting with suspected stroke, and new symptoms of less than 6 hours duration, will be defined to be experiencing “acute stroke” and triaged as at least an “ESI level 2,” or “emergent,” acuity, reflecting the critical, time-sensitive nature of making the correct diagnosis.

An acute stroke should be suspected in all patients with a sudden unexplained neurological change.

This includes (but is not limited to):

- focal weakness or numbness of the extremities or face
- speech or language changes
- changes in vision
- coordination deficits
- sudden unexplained headache, particularly if associated with altered level of consciousness

For patients unable to provide the time of onset of symptoms, or who awoke with symptoms, the time of onset is defined as the time when the patient was last known to be without new signs or symptoms.

A TIA should be considered in patients in whom the above symptoms occur with complete clinical resolution. It should be noted that a significant proportion (~30%) of patients given a clinical TIA diagnosis actually have MRI evidence of acute stroke, and thus have had a minor stroke, rather than a TIA, by the modern definition. The ABCD² scale is a simple clinical grading scale helpful in triaging TIA patients to the appropriate setting of



evaluation: observation, inpatient, or discharge with urgent specialized clinic follow-up. Higher ABCD² scores correlate with higher stroke risk. In validation cohorts, a score of 0–3 (low risk) carries a risk of 1.3% for a stroke within 2 days, a score of 4–5 (intermediate risk) carries a 4.1% risk, and a score of 6–7 carries an 8.1% risk.⁷ ABCD² scale specifics appear in Appendix D.

Current guidelines state that inpatient hospitalization is reasonable in TIA patients with an ABCD² score of ≥ 3 .^{2,8} Patients presenting more than 48 hours after their TIA symptoms may be able to instead be referred for a timely evaluation as an outpatient, in less than 1 week, given that 50% of subsequent stroke risk generally takes place in the first 48 hours after the event.⁹

Additionally, patients with any of the following are considered high-risk, and should be admitted as inpatients:

- atrial fibrillation
- carotid or intracranial stenoses/occlusions
- recurrent symptoms (crescendo TIA)
- imaging evidence of stroke, old or new
- known hypercoagulable state
- hemodynamic instability

Patients who do not meet the above criteria and have an ABCD² scale < 3 could be considered for observation and even urgent outpatient stroke neurologist evaluation. The key is that ALL of these patients need to be evaluated and treated, *including* with the recommended diagnostics below within 48 hours preferably, and optimally within 24 hours.^{2,8,10}

II. INITIAL EVALUATION

The initial evaluation of patients with a suspected acute stroke requires at a minimum, a targeted history and physical, standard labs and imaging, and specialty consultation when appropriate.

History

A targeted and brief medical history will be obtained. Time of onset of symptoms, or the time the patient was last seen normal and without symptoms, must be documented. Risk factors for stroke, as well as potential contraindications to thrombolytic therapy, must be ascertained and documented. An accurate medication list must be documented.

Physical exam

The physical exam will include a focused neurological exam that allows for recognizing and communicating findings necessary for evaluation and treatment of suspected stroke patients. Utilization of the NIH Stroke Scale or a comparable alternative is preferred. At a minimum, a standard emergent neurological exam for suspected stroke patients will include visual fields, motor, sensory, cerebellar, cognition, and speech and language evaluations. Gait testing should be performed by admitting or specialist physicians, but is also encouraged when possible in the emergent setting.

Diagnostics

At a minimum, the following will be obtained in a stat fashion:

- brain CT without contrast
- ECG and continuous cardiac monitoring
- continuous pulse oximetry
- bedside blood glucose
- serum electrolytes
- serum cardiac enzymes
- CBC including platelets
- PT/INR and PTT



Non-emergent laboratory testing for stroke/TIA work-up should include:

- fasting lipid panel
- Hemoglobin A1c

Additional laboratory testing at the discretion of the physician may include:

- HIV testing
- urine drug screen
- hypercoagulable panel
- ESR/CRP
- pregnancy testing

In selected patients, where available, CT angiography and/or perfusion studies should be obtained stat if endovascular intervention is being considered in lieu of or as an adjunct to IV thrombolysis. Such patients typically have high NIHSS reflective of large vessel occlusions. Immediate consultation with a Stroke Neurologist is recommended in these cases to help determine the appropriate diagnostic testing strategy and assessment of potential risks and benefits of all treatment options.

The delivery of IV thrombolysis is the priority for patients who otherwise meet criteria for IV thrombolysis, and should not be delayed to pursue additional imaging modalities or alternative treatments, including endovascular interventions. The evidence grade for IV-tPA is Class-I Level-A on the basis of multiple prospective randomized trials, while endovascular treatment of ischemic stroke is based on studies without the same degree of placebo control or as clear a consensus about its risks, benefits or indications.

In all cases, local protocols, developed as part of a “Stroke Alert,” “Code Stroke,” or similar process, may outline specific diagnostic pathways, including the role of advanced imaging and evaluation for potential invasive interventions. Where applicable, these protocols will determine the appropriate diagnostic pathways to follow, in consultation with Stroke Neurology or General Neurology as necessary.

All stroke and TIA patients should have a brain MRI without contrast unless contraindicated. This is optimally performed in < 24 hours, and often is helpful elucidating the stroke mechanism, and thus, helpful dictating further work-up as needed.

Non-emergent diagnostic testing should include imaging of cerebrovasculature including extracranial *and* intracranial arteries when not contraindicated. This can be accomplished with:

- CT angiogram head and neck
- *or* MR angiogram brain and neck
- *or* carotid duplex *in addition to* one of the above intracranial studies

In cases where cardiac pathology or a cardio-embolic stroke source is suspected, a trans-thoracic echocardiogram (TTE) should be considered. If there is a high suspicion of valvular disease, intracardiac thrombus, complex aortic plaque, patent foramen ovale in a patient < 60 years old, or an inadequate trans-thoracic study, a trans-esophageal echocardiogram (TEE) may be considered.

III. MANAGEMENT

Patients diagnosed with an acute ischemic stroke, who meet specific criteria for the administration of IV thrombolytics, will be administered IV-tPA.

Thrombolysis

Thrombolytic therapy with intravenous tPA (Alteplase) will be administered within 60 minutes of patient arrival, or initial evaluation, to all ischemic stroke patients who meet established criteria within 4.5 hours of symptom



onset, unless otherwise contraindicated. The time window specifies the maximum allowable timeframe for *initiation* of thrombolysis, not for *completion* of delivery.

The 1995 NINDS tPA study showed that, compared with placebo, patients given IV-tPA within 3 hours of symptom onset were at least 30% more likely to have minimal or no disability, with an 11–13% absolute increase of favorable outcomes on all rating scales.¹¹ This yielded a number needed to treat (NNT) of 8 to prevent one patient from having a poor outcome. Risk of symptomatic intracranial hemorrhage (sICH) within 36 hours was increased in the tPA group vs. placebo (6% vs. 1%). There was no difference in mortality between groups, however. The benefits of tPA were durable through 1 year in the NINDS population, and benefit was seen across stroke subtypes and etiologies.¹²

Since that study, other large observational trials have confirmed safety and efficacy of tPA in much larger populations across many institutions, both academic and community based.^{13,14} The recent IST-3 study also confirmed that the use of IV-tPA leads to statistically significant, clinically relevant improvements in functional outcome and health-related quality of life that are sustained for at least 18 months.¹⁵

When incorporating long term outcomes rather than short term effects across the entire spectrum of disability, and utilizing the current and more accurate definition of sICH, IV-tPA benefits 1 in 3 patients to some extent, and causes harm in only 3% of patients, with death or severe disability in 1% of patients.¹⁶⁻¹⁹

As with tPA in the 0–3 hour window, recent observational studies have confirmed the safety and efficacy of IV-tPA within the 3–4.5 hour window.²⁰ Subsequent statistical analyses outline approximately half the potential benefit of IV-tPA compared to the < 3 hour timeframe, with no increase in harm.²¹ IV-tPA is highly effective and safe for acute ischemic stroke therapy, and benefit strongly outweighs harm up to 4.5 hours with IV-tPA for acute ischemic stroke patients in a select population.²²

In summary, tPA is effective and safe for acute ischemic stroke therapy. Benefit strongly outweighs harm up to 4.5 hours with IV tPA for acute ischemic stroke patients. In the first 90 minutes, the NNT for any long term benefit is 3.6 patients. Between 91–180 minutes, the NNT is 4.3 patients, and between 180–270 minutes the NNT is 5.9 patients. Corresponding estimates of the NNT to cause harm are 65, 38, and 30 respectively.²³

While the goal is to deliver IV-tPA within 60 minutes of arrival in the ED, all efforts must be made for this to occur as rapidly as possible, with progressively diminishing benefit as time elapses.²⁴⁻²⁷

The criteria for administering IV-tPA in acute ischemic stroke for patients whose symptom onset is within 3 hours of initiating treatment are outlined in Appendix A.

The additional criteria for administering IV-tPA in acute ischemic stroke for patients whose symptom onset is within 3 to 4.5 hours of initiating treatment are outlined in Appendix B.

The specific guidelines for the actual administration of tPA, including treatment of complications, are provided in Appendix C.

Written consent is not required, but a full discussion with the decision maker should be carried out to the extent possible, and documented, including discussion of potential risks and benefits. In patients who do not qualify for, or refuse treatment with IV-tPA, it is particularly important to document all relevant decision making.²⁸

Blood pressure control

Patients with an acute ischemic stroke require prompt, but measured, control of blood pressure. A majority of patients with acute stroke have elevated blood pressure, and it is theorized that excessive reduction in blood pressure may compromise residual perfusion of ischemic brain. Conversely, elevated systolic pressures lead to concern for hemorrhage or CNS edema.



Patients undergoing treatment with IV-tPA require stabilization of blood pressure at a goal systolic pressure < 185 and diastolic < 110 mmHg. Tight control is required for patients undergoing thrombolysis to reduce the risk for complications of the therapy such as secondary hemorrhage.^{24,28}

Patients who are not undergoing IV thrombolysis are allowed a more liberal blood pressure target, with a target acute blood pressure goal of systolic < 200 mmHg and diastolic < 100 mmHg. AHA guidelines from 2013 suggest a goal < 220/120 mmHg based on conflicting and incomplete data,²⁸ but current practice predicated on more recent studies supports a lower target range.²⁹⁻³¹ Care should be taken not to acutely lower blood pressure beyond 15% of the initial presenting blood pressure in the first 24 hours.

Methods of lowering blood pressure:

In suspected acute ischemic stroke patients, IV, not oral, therapy is indicated.

Labetalol may be administered as 10 mg IV push every 5 minutes, in a total of three doses. If this does not achieve target reduction, initiate a continuous infusion.

In patients with bronchospasm or a stable heart rate < 60, use hydralazine 10 mg IV push every 5 minutes.

Enalaprilat may be administered, at an initial dose of 0.625 mg IV, or 1.25 mg IV, with repeat dosing every 6 hours.

Nicardipine is also effective as an infusion therapy at 5–15 mg/hr.

Nitrates, including nitroprusside, should not be used to treat hypertension in acute ischemic stroke.

Other management issues

Antiplatelet therapy:

An aspirin dose of 325 mg orally or by feeding tube within 24–48 hours is recommended in patients with acute ischemic stroke, or 300 mg per rectum if they have not passed a formal swallow evaluation and have no feeding tube. It is not necessary, nor is it thought to be beneficial, to administer antiplatelet drugs while in the Emergency Department. Patients undergoing IV thrombolysis or endovascular revascularization will have the administration of all antithrombotic medications delayed for at least 24 hours, and those should be started at that point once repeat imaging has established the absence of intracranial hemorrhage or other contraindication.

All TIA patients can be started on aspirin 325 mg orally if not contraindicated. Plavix 75 mg daily can be used in patients with an aspirin allergy.

Acute anticoagulation therapy:

There is no defined role for the use of early parenteral anticoagulation in acute ischemic stroke,²⁴ with any benefit offset by potential harm from hemorrhage,³² and it is not recommended. Anticoagulation is further contraindicated for 24 hours after the administration of IV thrombolytic therapy. Specific further indications should be discussed with specialist consultants.

Statin therapy:

There is no defined acute role for statin therapy in stroke or TIA patients during the emergent or initial evaluation phase, but continuing outpatient statins is recommended when swallowing safely or when a feeding tube is placed. High dose, high potency statin therapy (e.g. atorvastatin 80 mg daily) should be considered in all stroke or TIA patients with LDL > 100, or in diabetic stroke patients or patients with presumed atherosclerotic mechanism of stroke.^{28,33}

Swallowing:

Up to three quarters of acute stroke patients can be expected to have some amount of dysphagia and subsequent risk for aspiration and pneumonia. Patients should be immediately made NPO during the acute stroke



evaluation, and must continue NPO status until a formal evaluation of aspiration risk is conducted. Unlike acute coronary syndromes, there is no defined benefit to administering an aspirin in the Emergency Department, and any oral intake should be weighed against the potential for aspiration.²⁸

*General supportive care:*²⁸

Peripheral oxygen saturation will be maintained at $\geq 94\%$ as needed with oxygen therapy.

The effectiveness of treating fever in acute stroke patients is not established, but it is generally agreed that sources of fever should be treated and antipyretic agents should be given to lower temperatures in febrile patients with acute stroke.

Hyperglycemia in acute stroke will be addressed and treated in the ED. Serum glucose should be reduced to a goal of 140–180mg/dL.

Hypoglycemia should be avoided and blood glucose $< 60\text{mg/dL}$ should be treated with the goal of normoglycemia up to 140–180mg/dL.

Euvolemia should be achieved, avoiding hypotonic or dextrose containing fluids unless specifically indicated.

Fall precautions will be initiated in the ED.

A Rehab Liaison will be consulted upon admission to initiate consideration of acute rehab needs.

Stroke education:

Prior to discharge, all stroke and TIA patients need education regarding stroke symptoms, the need for emergent evaluation, and possible lifestyle modifications. When possible, educational materials should be provided, and education needs documented by nursing staff or physicians.

IV. DISPOSITION

Consults

In cases where specialty consultation is desired, but the facility lacks specialty coverage, providers are directed to utilize Outreach (Banner Health Transfer Center—BHTC) in Arizona, or local protocols in all other states, to facilitate discussion with an appropriate consultant, and to assist in making evaluation, treatment, and disposition decisions. It should be noted that specialist consultation in this context has been demonstrated to reduce mortality rates and improve clinical outcomes.^{34,35}

Admission criteria

All acute ischemic strokes presenting to the ED will be admitted.

While telemetry should be the default initial consideration for all stroke patients, patients treated with IV-tPA must be admitted to an ICU level of care for at least 24 hours.

Moderate- and high-risk TIA patients should not be discharged from the emergency room, and can be considered for either observation status or inpatient status as above. Low-risk TIA patients can be considered for urgent (< 48 hours) evaluation in specialist TIA clinics, if the above testing is arranged prior to discharge, and appropriate therapies have been initiated.

Transfer guidelines

In cases where the ED provider suspects a patient may need transfer for a higher level of care, BHTC, or local outreach mechanisms, will be notified as early as possible to facilitate identification of an appropriate receiving provider and facility.



Prior to transfer, the ED provider will determine, in consultation with the receiving provider, the need for any imaging, medications, or procedures that should be carried out prior to transfer.

If IV-tPA is indicated in an acute ischemic stroke patient for who transfer to a higher level of care will be required, administration of tPA should begin at the originating facility. Therapy must not be delayed pending transfer or arrival at the destination facility. In cases where the transportation crew is unable or unwilling to continue thrombolytic therapy during transport, IV-tPA will be initiated and completed prior to transfer.

Note the management of patients whose evaluation leads to the determination or suspicion of *intracerebral hemorrhage* is discussed in the *Initial Evaluation and Treatment of Patients with Hemorrhagic Stroke - Adult Clinical Practice*, however their triage and initial evaluation is the same.



REFERENCES:

1. Go, A. S. et al. Heart disease and stroke statistics--2013 update: a report from the American Heart Association. *Circulation* 127, e6–e245 (2013).
2. Easton, J. D. et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. *Stroke* 40, 2276–2293 (2009).
3. Johnston, S. C. Clinical practice. Transient ischemic attack. *N Engl J Med* 347, 1687–1692 (2002).
4. Rothwell, P. M. et al. Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. *Lancet* 370, 1432–1442 (2007).
5. Luengo-Fernandez, R., Gray, A. M. & Rothwell, P. M. Effect of urgent treatment for transient ischaemic attack and minor stroke on disability and hospital costs (EXPRESS study): a prospective population-based sequential comparison. *Lancet Neurol* 8, 235–243 (2009).
6. Lavallée, P. C. et al. A transient ischaemic attack clinic with round-the-clock access (SOS-TIA): feasibility and effects. *Lancet Neurol* 6, 953–960 (2007).
7. Johnston, S. C. et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. *Lancet* 369, 283–292 (2007).
8. Johnston, S. C. et al. National stroke association recommendations for systems of care for transient ischemic attack. *Ann Neurol* 69, 872–877 (2011).
9. Johnston, S. C. et al. National Stroke Association guidelines for the management of transient ischemic attacks. *Ann Neurol* 60, 301–313 (2006).
10. Furie, K. L. et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the american heart association/american stroke association. *Stroke* 42, 227–276 (2011).
11. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. *N Engl J Med* 333, 1581–1587 (1995).
12. Kwiatkowski, T. G. et al. Effects of tissue plasminogen activator for acute ischemic stroke at one year. National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Study Group. *N Engl J Med* 340, 1781–1787 (1999).
13. Hill, M. D., Buchan, A. M. & Canadian Alteplase for Stroke Effectiveness Study CASES Investigators. Thrombolysis for acute ischemic stroke: results of the Canadian Alteplase for Stroke Effectiveness Study. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne* 172, 1307–1312 (2005).
14. Wahlgren, N. 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* 369, 275–282 (2007).
15. IST-3 collaborative group. Effect of thrombolysis with alteplase within 6 h of acute ischaemic stroke on long-term outcomes (the third International Stroke Trial [IST-3]): 18-month follow-up of a randomised controlled trial. *Lancet Neurol* 12, 768–776 (2013).
16. Saver, J. L. Number needed to treat estimates incorporating effects over the entire range of clinical outcomes: novel derivation method and application to thrombolytic therapy for acute stroke. *Arch Neurol* 61, 1066–1070 (2004).
17. Saver, J. L. Hemorrhage after thrombolytic therapy for stroke: the clinically relevant number needed to harm. *Stroke* 38, 2279–2283 (2007).
18. Saver, J. L., Gornbein, J. & Starkman, S. Graphic reanalysis of the two NINDS-tPA trials confirms substantial treatment benefit. *Stroke* 41, 2381–2390 (2010).
19. Gadhia, J. et al. Assessment and Improvement of Figures to Visually Convey Benefit and Risk of Stroke Thrombolysis. *Stroke* 41, 300 (2010).
20. Wahlgren, N. et al. Thrombolysis with alteplase 3-4.5 h after acute ischaemic stroke (SITS-ISTR): an observational study. *Lancet* 372, 1303–1309 (2008).
21. Saver, J. L. et al. Number needed to treat to benefit and to harm for intravenous tissue plasminogen activator therapy in the 3- to 4.5-hour window: joint outcome table analysis of the ECASS 3 trial. *Stroke* 40, 2433–2437 (2009).



22. Hacke, W. et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 359, 1317–1329 (2008).
23. Lansberg, M. G., Schrooten, M., Bluhmki, E., Thijs, V. N. & Saver, J. L. Treatment time-specific number needed to treat estimates for tissue plasminogen activator therapy in acute stroke based on shifts over the entire range of the modified Rankin Scale. *Stroke* 40, 2079–2084 (2009).
24. Lansberg, M. G. et al. Antithrombotic and thrombolytic therapy for ischemic stroke: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 141, e601S–36S (2012).
25. Marler, J. R. et al. Early stroke treatment associated with better outcome: the NINDS rt-PA stroke study. *Neurology* 55, 1649–1655 (2000).
26. Hacke, W. et al. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet* 363, 768–774 (2004).
27. Saver, J. L. et al. Time to treatment with intravenous tissue plasminogen activator and outcome from acute ischemic stroke. *JAMA* 309, 2480–2488 (2013).
28. Guidelines for the Early Management of Patients With Acute Ischemic Stroke : A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. 1–87 (2013). doi:10.1161/STR.0b013e318284056a/-/DC1
29. Geeganage, C. M. & Bath, P. M. W. Relationship between therapeutic changes in blood pressure and outcomes in acute stroke: a metaregression. *Hypertension* 54, 775–781 (2009).
30. Geeganage, C. et al. Relationship between baseline blood pressure parameters (including mean pressure, pulse pressure, and variability) and early outcome after stroke: data from the Tinzaparin in Acute Ischaemic Stroke Trial (TAIST). *Stroke* 42, 491–493 (2011).
31. Potter, J. F. et al. Controlling hypertension and hypotension immediately post-stroke (CHHIPS): a randomised, placebo-controlled, double-blind pilot trial. *Lancet Neurol* 8, 48–56 (2009).
32. Sandercock, P. A. G., Counsell, C. & Kamal, A. K. Anticoagulants for acute ischaemic stroke. *Cochrane Database Syst Rev* CD000024 (2008). doi:10.1002/14651858.CD000024.pub3
33. Amarenco, P. et al. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med* 355, 549–559 (2006).
34. Mitchell, J. B. et al. What role do neurologists play in determining the costs and outcomes of stroke patients? *Stroke* 27, 1937–1943 (1996).
35. Goldstein, L. B., Matchar, D. B., Hoff-Lindquist, J., Samsa, G. P. & Horner, R. D. VA Stroke Study: neurologist care is associated with increased testing but improved outcomes. *Neurology* 61, 792–796 (2003).
36. del Zoppo, G. J., Saver, J. L., Jauch, E. C., Adams, H. P. American Heart Association Stroke Council. 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* 40, 2945–2948 (2009).

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Stroke

Ischemic stroke

TIA / transient ischemic attack

tPA / Alteplase

Thrombolysis

Hypertension

Endovascular



APPENDICES:

APPENDIX A—CRITERIA FOR ADMINISTRATION OF IV-tPA IN STROKE PATIENTS WITHIN 3 HOURS OF SYMPTOM ONSET OR TIME LAST KNOWN TO BE SYMPTOM FREE:²⁸

(Note that treatment with tPA should be initiated, but *does not need to be completed*, within 3 hours of symptom onset)

Guidelines for IV-tPA administration:

- Time of symptom onset should be < 3 hours before beginning treatment
- Onset time is defined as either witnessed onset of symptoms or the time last known normal if the symptom onset was not witnessed
- When symptoms have *completely* resolved before recurring, the clock restarts
- Treatment with tPA does not need to be completed before 3 hours
- Additional guidelines may be considered below for symptoms of > 3 hours duration
- In patients without recent use of anticoagulants, treatment with IV-tPA can be initiated before availability of coagulation test results but should be discontinued if INR is > 1.7 or PT/PTT are abnormally prolonged
- In patients without history of thrombocytopenia, treatment with IV-tPA can be initiated before availability of platelet count but should be discontinued if platelet count is < 100,000/mm³
- Patient or family members are counseled and understand the potential risks and benefits. Written consent is not necessary but a full discussion with the decision maker should be carried out to the extent possible and documented including potential risks and benefits.
- Goal is tPA delivery in less than 60 minutes from initial patient contact; better outcomes are achieved with more rapid drug delivery.

Indications for IV-tPA administration:

- Age ≥ 18
- Diagnosis of ischemic stroke causing measurable neurologic deficit. No specific NIHSS high/low cutoffs are recommended, but caution is advised with severe strokes (NIHSS > 22).
- Onset of symptoms is less than 3 hours from treatment time. Additional criteria can be applied for selected patients with symptoms of 3–4.5 hours duration, and are outlined in Appendix B.

Contraindications:

- Significant head trauma or prior stroke in the preceding 3 months
- Symptoms suggesting subarachnoid or other intracranial hemorrhage
- Arterial puncture at a non-compressible site in the past 7 days
- History of intracranial hemorrhage
- History of intracranial neoplasm, arteriovenous malformation, or aneurysm. *Presence of aneurysm or AVM should be discussed with specialist but treatment may still be considered.*
- Intracranial or intraspinal surgery in the past 3 months
- Blood pressure > 185 mmHg Systolic and > 110 mmHg Diastolic. Can be treated to < 185/110 mmHg. tPA should not be considered if BP of < 185/110 mmHg cannot be reliably assured.
- Active bleeding or significant acute trauma
- Platelet count less than 100,000/mcL
- Heparin in the previous 48 hours AND an elevated aPTT above upper limit normal. Cannot be reversed to meet this criterion.
- Current use of anticoagulation with INR > 1.7. Anticoagulation cannot be reversed to meet this criterion.



- Use of oral direct thrombin inhibitors (dabigatran) or direct factor Xa inhibitors (rivaroxaban, apixaban) within in last 48 hours. *Can be discussed/considered with specialist consultant if last dose > 48 hours and GFR is normal (> 50) or last dose was 3–5 days ago with reduced GFR (< 50).*
- Blood glucose less than 50 mg/dl and greater than 400 mg/dl. *Can be treated to appropriate range prior to administration.*
- CT head demonstrates early evidence (hypodensity) of a multilobar infarction > 1/3 cerebral hemisphere
- CT head with evidence of hemorrhage
- Lumbar puncture in the preceding 7 days
- Treatment with anticoagulation doses of LMWH (Lovenox) for 48 hours. DVT prophylaxis doses of Heparin or LMWH are OK.
- Prior adverse reaction or allergy to tPA

Relative contraindications for 3 hour window:

Recent experience suggests that under some circumstances—with careful consideration and weighing of potential risk vs. benefit—patients may receive IV-tPA despite one or more relative contraindications.²⁸

- Minor or rapidly improving neurologic signs, but if meaningful deficits are still present tPA should be considered
- Pregnancy
- Seizure at onset with postictal residual neurological impairment; the postictal impairment should not be the sole new neurologic deficit however.
- Major surgery in the past 14 days or serious trauma
- GI or urinary tract hemorrhage in the past 21 days
- Myocardial infarction in the preceding 3 months



APPENDIX B—ADDITIONAL CRITERIA FOR tPA ADMINISTRATION WITHIN 3 TO 4.5 HOURS:³⁶

All considerations in Appendix A apply, with the additional criteria of:

Relative contraindications for 3–4.5 hour window:

- Age > 80
- NIHSS > 25
- On any form of anticoagulation, regardless of INR or other coagulation markers
- Prior history of stroke in a patient with diabetes
- Imaging demonstrates early evidence of infarction > 1/3 of the MCA territory

*Use of IV-tPA between 3 and 4.5 hours is supported by scientific consensus of the AHA/ASA, but FDA labeling has not been updated to reflect that recommendation. Individual centers with locally supportive clinical practice guidelines may use IV-tPA according to these additional criteria.

APPENDIX C—ADMINISTRATION GUIDELINES FOR tPA:

After determining that a patient is an appropriate candidate for IV-tPA, administer as follows:

- initial bolus dose of 0.09 mg/kg over 1 minute (10% of the total 0.9 mg/kg dose)
- continuous infusion dose of 0.81 mg/kg over 60 minutes (90% of the total 0.9 mg/kg dose)
- the maximum total dose, including bolus, is not to exceed 90 mg

Infusion of tPA is to be stopped immediately and the treating physician notified for any potential complications, including:

- sudden decrease in level of consciousness
- headache
- nausea or vomiting
- new neurologic deficit
- evidence of bleeding
- evidence of allergic reaction (e.g. tongue swelling)

Vital signs and neurologic status are to be monitored and documented q 15 minutes during the tPA infusion and until 2 hours after treatment is initiated, then q 30 minutes for the following 6 hours, then at least hourly for the remainder of 24 hours after treatment. Increase the frequency of vital signs if BP > 180/105 mmHg.

Monitor at all times during administration for signs and symptoms of possible hemorrhage. If hemorrhage is suspected clinically, stop administration of tPA and obtain a stat head CT. If the head CT confirms a hemorrhage, proceed as follows:

- type and screen if not already done
- administer cryoprecipitate 1 bag per 10 kg patient weight (typical 6–10 bags)
- administer platelets 1 unit per 10 kg patient weight (typically 6–10 units)
- immediate consultation with Neurology and Neurosurgery

Further post-tPA care includes:

- admission to ICU level of care for at least 24 hours
- no use of heparinoids, antiplatelet agents, or any other form of antithrombotic for 24 hours
- no nasogastric tube, intramuscular injections or arterial punctures for 24 hours



- delay Foley placement for as long as possible (if the patient can be safely managed) for the first 24 hours
- during the first 24 hours after the tPA infusion has been started, the placement of venous catheters should be delayed if possible, and if required, inserted with direct visualization of the vessel at a compressible site

Appendix D — ABCD² scale for the assessment of stroke risk after a TIA:⁷

The ABCD² score is a risk assessment tool designed to improve the prediction of short-term stroke risk after a transient ischemic attack (TIA). The score is optimized to predict the risk of stroke within 2 days after a TIA, but also predicts stroke risk within 90 days. The ABCD² score is calculated by summing up points for five independent factors.

Risk Factor	Score
Age ≥ 60 years	1
Blood Pressure Systolic BP ≥ 140 mmHg OR diastolic BP ≥ 90 mmHg	1
Clinical features of TIA (choose one) Unilateral weakness with or without speech impairment	2
Speech impairment without unilateral weakness	1
Duration TIA duration ≥ 60 minutes	2
TIA duration 10-59 minutes	1
Diabetes	1

The authors of the ABCD² score made the following recommendations for hospital observation/admission:

ABCD2 Score	2-day Stroke Risk	Comment
0-3	1.0%	Hospital observation may be unnecessary without another indication (e.g., new atrial fibrillation)
4-5	4.1%	Hospital observation justified in most situations
6-7	8.1%	Hospital observation worthwhile