# rtPA Inclusion and Exclusion Criteria

## Pearls

- Determine tPA eligibility as soon as possible after arrival
- Immediately initiate discussion of consent if patient is a candidate for tPA.
- Do not forget basics for good stroke management (i.e., glycemic control, BP control, seizure precautions, etc.)
- Be familiar with additional exclusions for patients in the 3-4.5 hour window.

According to current practice guidelines from the American Heart Association/American Stroke (AHA/ASA) (2019), the treatment of acute ischemic stroke (AIS) should include careful consideration of thrombolysis. For eligible patients with AIS, IV tPA is the first-line therapy, provided that treatment is initiated within 4.5 hours of symptom onset or the time patients were last known to be well (i.e., at neurologic baseline). Because the benefit of rRecombinant tissue plasminogen activator (rtPA) is time dependent, it is critical to treat patients as quickly as possible.

Review the Eligibility Recommendations for IV rtPA in Patients with AIS.

| **Indications (COR I)** | |
|---|---|
| Within 3 h | IV rtPA (0.9 mg/kg, maximum dose 90 mg over 60 min with initial 10% of dose given as bolus over 1 min) is recommended for selected patients who may be treated within 3 h of ischemic stroke symptom onset or patient last known well or at baseline state. Physicians should review the criteria outlined in this table to determine patient eligibility. (COR I; LOE A) |
| Within 3 h–<br>Age | For otherwise medically eligible patients ≥18 y of age, IV rtPA administration within 3 h is equally recommended for patients ≤80 and >80 y of age. (COR I; LOE A) |
| Within 3 h–Severe stroke | For severe stroke, IV rtPA is indicated within 3 h from symptom onset of ischemic stroke. Despite increased risk of hemorrhagic transformation, there is still proven clinical benefit for patients with severe stroke symptoms. (COR I; LOE A) |
| Within 3 h–<br>Mild disabling stroke | For otherwise eligible patients with mild but disabling stroke symptoms, IV rtPA is recommended for patients who can be treated within 3 h of ischemic stroke symptom onset or patient last known well or at baseline state (COR I; LOE B-R)‡ |
| 3–4.5 h | IV rtPA (0.9 mg/kg, maximum dose 90 mg over 60 min with initial 10% of dose given as bolus over 1 min) is also recommended for selected patients who can be treated within 3 and 4.5 h of ischemic stroke symptom onset or patient last known well. Physicians should review the criteria outlined in this table to determine patient eligibility. (COR I; LOE B-R) |
| 3–4.5 h–<br>Age | IV rtPA treatment in the 3- to 4.5-h time window is recommended for those patients ≤80 y of age, without a history of both diabetes mellitus and prior stroke, NIHSS score ≤25, not taking any OACs, and without imaging evidence of ischemic injury involving more than one-third of the MCA territory. (COR I; LOE B-R) |
| Urgency | Treatment should be initiated as quickly as possible within the above-listed time frames because time to treatment is strongly associated with outcomes. (COR I; LOE A) |

| Indications (COR I) | |
|---|---|
| BP | IV rtPA is recommended in patients with BP <185/110 mm Hg and in those patients whose BP can be lowered safely to this level with antihypertensive agents, with the physician assessing the stability of the BP before starting IV rtPA. (COR I; LOE B-NR)§ |
| Blood glucose | IV rtPA is recommended in otherwise eligible patients with initial glucose levels >50 mg/dL. (COR I; LOE A) |
| CT | IV rtPA administration is recommended in the setting of early ischemic changes on NCCT of mild to moderate extent (other than frank hypodensity). (COR I; LOE A) |
| Prior antiplatelet therapy | IV rtPA is recommended for patients taking antiplatelet drug monotherapy before stroke on the basis of evidence that the benefit of rtPA outweighs a possible small increased risk of sICH. (COR I; LOE A)<br><br>IV rtPA is recommended for patients taking antiplatelet drug combination therapy (eg, aspirin and clopidogrel) before stroke on the basis of evidence that the benefit of rtPA outweighs a probable increased risk of sICH. (COR I; LOE B-NR) |
| End-stage renal disease | In patients with end-stage renal disease on hemodialysis and normal aPTT, IV rtPA is recommended. (COR I; LOE C-LD) However, those with elevated aPTT may have elevated risk for hemorrhagic complications. |

| Additional recommendations for treatment with IV rtPA for patients with AIS (COR IIa) | And (COR IIb) |
|---|---|
| 3 to 4.5 h–Age | For patients >80 y of age presenting in the 3- to 4.5-h window, IV rtPA is safe and can be as effective as in younger patients. (COR IIa; LOE B-NR) |
| 3 to 4.5 h–Diabetes mellitus and prior stroke | In AIS patients with prior stroke and diabetes mellitus presenting in the 3- to 4.5- h window, IV rtPA may be as effective as treatment in the 0- to 3-h window and may be a reasonable option. (COR IIb; LOE B-NR) |
| 3 to 4.5 h–Severe stroke | The benefit of IV rtPA between 3 and 4.5 h from symptom onset for patients with very severe stroke symptoms (NIHSS score >25) is uncertain. (COR IIb; LOE C-LD) |
| 3 to 4.5 h–Mild disabling stroke | For otherwise eligible patients with mild disabling stroke, IV rtPA may be reasonable for patients who can be treated within 3 and 4.5 h of ischemic stroke symptom onset or patient last known well or at baseline state. (COR IIb; LOE B-NR) |
| Wake-up and unknown time of onset | IV rtPA (0.9 mg/kg, maximum dose 90 mg over 60 min with initial 10% of dose given as bolus over 1 min) administered within 4.5 h of stroke symptom recognition can be beneficial in patients with AIS who awake with stroke symptoms or have unclear time of onset >4.5 h from last known well or at baseline state and who have a DW-MRI lesion smaller than one-third of the MCA territory and no visible signal change on FLAIR. (COR IIa; LOE B-R) |

| Additional recommendations for treatment with IV rtPA for patients with AIS (COR IIa) | And (COR IIb) |
|---|---|
| Preexisting disability | Preexisting disability does not seem to independently increase the risk of sICH after IV rtPA, but it may be associated with less neurological improvement and higher mortality. Therapy with IV rtPA for acute stroke patients with preexisting disability (mRS score ≥2) may be reasonable, but decisions should take into account relevant factors, including quality of life, social support, place of residence, need for a caregiver, patients' and families' preferences, and goals of care.†(COR IIb; LOE B-NR)<br><br>Patients with preexisting dementia may benefit from IV rtPA. Individual considerations such as life expectancy and premorbid level of function are important to determine whether rtPA may offer a clinically meaningful benefit.† (COR IIb; LOE B-NR) |
| Early improvement | IV rtPA treatment is reasonable for patients who present with moderate to severe ischemic stroke and demonstrate early improvement but remain moderately impaired and potentially disabled in the judgment of the examiner. (COR IIa; LOE A) |
| Seizure at onset | IV rtPA is reasonable in patients with a seizure at the time of onset of acute stroke if evidence suggests that residual impairments are secondary to stroke and not a postictal phenomenon. (COR IIa; LOE C-LD) |
| Blood glucose | IV rtPA in patients with AIS who present with initial glucose levels <50 or >400 mg/dL that are subsequently normalized and who are otherwise eligible may be reasonable (COR IIb; LOE C-LD) |
| Coagulopathy | IV rtPA may be reasonable in patients who have a history of warfarin use and an INR ≤1.7 or a PT <15 s. (COR IIb; LOE B-NR) The safety and efficacy of IV rtPA for acute stroke patients with a clinical history of potential bleeding diathesis or coagulopathy are unknown. IV rtPA may be considered on a case-by-case basis. (COR IIb; LOE C-EO) |
| Dural puncture | IV rtPA may be considered for patients who present with AIS, even in instances when they may have undergone a lumbar dural puncture in the preceding 7 d. (COR IIb; LOE C-EO) |
| Arterial puncture | The safety and efficacy of administering IV rtPA to acute stroke patients who have had an arterial puncture of a noncompressible blood vessel in the 7 d preceding stroke symptoms are uncertain. (COR IIb; LOE C-LD) |
| Recent major trauma | In AIS patients with recent major trauma (within 14 d) not involving the head, IV rtPA may be carefully considered, with the risks of bleeding from injuries related to the trauma weighed against the severity and potential disability from the ischemic stroke. (COR IIb; LOE C-LD) |
| Recent major surgery | Use of IV rtPA in carefully selected patients presenting with AIS who have undergone a major surgery in the preceding 14 d may be considered, but the potential increased risk of surgical-site hemorrhage should be weighed against the anticipated benefits of reduced stroke related neurological deficits.†(COR IIb; LOE C-LD) |

| Additional recommendations for treatment with IV rtPA for patients with AIS (COR IIa) | And (COR IIb) |
|---|---|
| GI and genitourinary bleeding | Reported literature details a low bleeding risk with IV rtPA administration in the setting of past GI/genitourinary bleeding. Administration of IV rtPA in this patient population may be reasonable. (COR IIb; LOE C-LD (Note: rtPA administration within 21 d of a GI bleeding event is not recommended; see Contraindications.) |
| Menstruation | IV rtPA is probably indicated in women who are menstruating who present with AIS and do not have a history of menorrhagia. However, women should be warned that rtPA treatment could increase the degree of menstrual flow. (COR IIa; LOE C-EO)<br><br>When there is a history of recent or active vaginal bleeding causing clinically significant anemia, then emergency consultation with a gynecologist is probably indicated before a decision about IV rtPA is made. (COR IIa; LOE C-EO)<br><br>Because the potential benefits of IV rtPA probably outweigh the risks of serious bleeding in patients with recent or active history of menorrhagia without clinically significant anemia or hypotension, IV rtPA administration may be considered. (COR IIb; LOE C-LD) |
| Extracranial cervical dissections | IV rtPA in AIS known or suspected to be associated with extracranial cervical arterial dissection is reasonably safe within 4.5 h and probably recommended. (COR IIa; LOE C-LD) |
| Intracranial arterial dissection | IV rtPA usefulness and hemorrhagic risk in AIS known or suspected to be associated with intracranial arterial dissection remain unknown, uncertain and not well established. (COR IIb; LOE C-LD) |
| Unruptured intracranial aneurysm | For patients presenting with AIS who are known to harbor a small or moderate-sized (<10 mm) unruptured and unsecured intracranial aneurysm, administration of IV rtPA is reasonable and probably recommended. (COR IIa; LOE C-LD)<br><br>Usefulness and risk of IV rtPA in patients with AIS who harbor a giant unruptured and unsecured intracranial aneurysm are not well established. (COR IIb; LOE C-LD) |
| Intracranial vascular malformations | For patients presenting with AIS who are known to harbor an unruptured and untreated intracranial vascular malformation the usefulness and risks of administration of IV rtPA are not well established.† (COR IIb; LOE C-LD)§<br><br>Because of the increased risk of ICH in this population of patients, IV rtPA may be considered in patients with stroke with severe neurological deficits and a high likelihood of morbidity and mortality to outweigh the anticipated risk of ICH. (COR IIb; LOE C-LD) |

| Additional recommendations for treatment with IV rtPA for patients with AIS (COR IIa) | And (COR IIb) |
|---|---|
| CMBs | In otherwise eligible patients who have previously had a small number (1–10) of CMBs demonstrated on MRI, administration of IV rtPA is reasonable. (COR IIa; Level B-NR)<br><br>In otherwise eligible patients who have previously had a high burden of CMBs (>10) demonstrated on MRI, treatment with IV rtPA may be associated with an increased risk of sICH, and the benefits of treatment are uncertain. Treatment may be reasonable if there is the potential for substantial benefit. (COR IIb; Level B-NR) |
| Concomitant tirofiban, epifibatide | The efficacy of the IV glycoprotein IIb/IIIa inhibitors tirofiban and eptifibatide coadministered with IV rtPA is not well established. (COR IIb; Level B-NR) |
| Extra-axial intracranial neoplasms | IV rtPA treatment is probably recommended for patients with AIS who harbor an extra-axial intracranial neoplasm. (COR IIa; LOE C-EO) |
| Acute MI | For patients presenting with concurrent AIS and acute MI, treatment with IV rtPA at the dose appropriate for cerebral ischemia, followed by percutaneous coronary angioplasty and stenting if indicated, is reasonable. (COR IIa; LOE C-EO)§ |
| Recent MI | For patients presenting with AIS and a history of recent MI in the past 3 mo, treating the ischemic stroke with IV rtPA is reasonable if the recent MI was non-STEMI. (COR IIa; LOE C-LD)<br><br>For patients presenting with AIS and a history of recent MI in the past 3 mo, treating the ischemic stroke with IV rtPA is reasonable if the recent MI was a STEMI involving the right or inferior myocardium. (COR IIa; LOE C-LD)<br><br>For patients presenting with AIS and a history of recent MI in the past 3 mo, treating the ischemic stroke with IV rtPA may be reasonable if the recent MI was a STEMI involving the left anterior myocardium. (COR IIb; LOE C-LD) |
| Acute pericarditis | For patients with major AIS likely to produce severe disability and acute pericarditis, treatment with IV rtPA may be reasonable† (COR IIb; LOE C-EO)§; urgent consultation with a cardiologist is recommended in this situation.<br><br>For patients presenting with moderate AIS likely to produce mild disability and acute pericarditis, treatment with IV rtPA is of uncertain net benefit. (COR IIb; LOE C-EO) |
| Left atrial or ventricular thrombus | For patients with major AIS likely to produce severe disability and known left atrial or ventricular thrombus, treatment with IV rtPA may be reasonable. (COR IIb; LOE C-LD)<br><br>For patients presenting with moderate AIS likely to produce mild disability and known left atrial or ventricular thrombus, treatment with IV rtPA is of uncertain net benefit. (COR IIb; LOE C-LD) |

| Additional recommendations for treatment with IV rtPA for patients with AIS (COR IIa) | And (COR IIb) |
|---|---|
| Other cardiac diseases | For patients with major AIS likely to produce severe disability and cardiac myxoma, treatment with IV rtPA may be reasonable. (COR IIb; LOE C-LD)<br><br>For patients presenting with major AIS likely to produce severe disability and papillary fibroelastoma, treatment with IV rtPA may be reasonable. (COR IIb; LOE C-LD) |
| Procedural stroke | IV rtPA is reasonable for the treatment of AIS complications of cardiac or cerebral angiographic procedures, depending on the usual eligibility criteria. (COR IIa; LOE A) |
| Systemic malignancy | The safety and efficacy of IV rtPA in patients with current malignancy are not well established. (COR IIb; LOE C-LD)<br><br>Patients with systemic malignancy and reasonable (>6 mo) life expectancy may benefit from IV rtPA if other contraindications, such as coagulation abnormalities, recent surgery, or systemic bleeding do not coexist. |
| Pregnancy | IV rtPA administration may be considered in pregnancy when the anticipated benefits of treating moderate or severe stroke outweigh the anticipated increased risks of uterine bleeding. (COR IIb; LOE C-LD)<br><br>The safety and efficacy of IV rtPA in the early postpartum period (<14 d after delivery) have not been well established. (COR IIb; LOE C-LD) |
| Ophthalmological conditions | Use of IV rtPA in patients presenting with AIS who have a history of diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic conditions is reasonable to recommend, but the potential increased risk of visual loss should be weighed against the anticipated benefits of reduced stroke-related neurological deficits. (COR IIa; LOE B-NR) |
| Sickle cell disease | IV rtPA for adults presenting with an AIS with known sickle cell disease can be beneficial. (COR IIa; LOE B-NR) |
| Hyperdense MCA sign | In patients with a hyperdense MCA sign, IV rtPA can be beneficial. (COR IIa; LOE B-NR) |
| Illicit drug use | Treating clinicians should be aware that illicit drug use may be a contributing factor to incident stroke. IV rtPA is reasonable in instances of illicit drug use–associated AIS in patients with no other exclusions.† (COR IIa; LOE C-LD) |
| Stroke mimics | The risk of symptomatic intracranial hemorrhage in the stroke mimic population is quite low; thus, starting IV rtPA is probably recommended in preference over delaying treatment to pursue additional diagnostic studies. (COR IIa; LOE B-NR) |

| Contraindications (COR III: No Benefit) | And (COR III: Harm) |
|---|---|
| 0- to 3-h–<br>Mild nondisabling stroke | For otherwise eligible patients with mild nondisabling stroke (NIHSS score 0–5), IV rtPA is not recommended for patients who could be treated within 3 h of ischemic stroke symptom onset or patient last known well or at baseline state. (COR III: No Benefit, LOE B-R) |
| 3- to 4.5-h window–<br>Mild nondisabling stroke | For otherwise eligible patients with mild nondisabling stroke (NIHSS score 0–5), IV rtPA is not recommended for patients who could be treated within 3 and 4.5 h of ischemic stroke symptom onset or patient last known well or at baseline state. (COR III: No Benefit, LOE C-LD) |
| CT | There remains insufficient evidence to identify a threshold of hypoattenuation severity or extent that affects treatment response to rtPA. However, administering IV rtPA to patients whose CT brain imaging exhibits extensive regions of clear hypoattenuation is not recommended. These patients have a poor prognosis despite IV rtPA, and severe hypoattenuation defined as obvious hypodensity represents irreversible injury. (COR III: No Benefit; LOE A) |
| ICH | IV rtPA should not be administered to a patient whose CT reveals an acute intracranial hemorrhage. (COR III: Harm; LOE C-EO) |
| Ischemic stroke within 3 mo | Use of IV rtPA in patients presenting with AIS who have had a prior ischemic stroke within 3 mo may be harmful. (COR III: Harm; LOE B-NR) |
| Severe head trauma within 3 mo | In AIS patients with recent severe head trauma (within 3 mo), IV rtPA is contraindicated. (COR III: Harm; LOE C-EO) |
| Acute head trauma | Given the possibility of bleeding complications from the underlying severe head trauma, IV rtPA should not be administered in posttraumatic infarction that occurs during the acute in-hospital phase. (COR III: Harm; LOE C-EO) |
| Intracranial/intraspinal surgery within 3 mo | For patients with AIS and a history of intracranial/spinal surgery within the prior 3 mo, IV rtPA is potentially harmful. (COR III: Harm; LOE C-EO) |
| History of intracranial hemorrhage | IV rtPA administration in patients who have a history of intracranial hemorrhage is potentially harmful. (COR III: Harm; LOE C-EO) |
| Subarachnoid hemorrhage | IV rtPA is contraindicated in patients presenting with symptoms and signs most consistent with an SAH. (COR III: Harm; LOE C-EO) |
| GI malignancy or GI bleed within 21 d | Patients with a structural GI malignancy or recent bleeding event within 21 d of their stroke event should be considered high risk, and IV rtPA administration is potentially harmful. (COR III: Harm; LOE C-EO) |

| Contraindications (COR III: No Benefit) | And (COR III: Harm) |
|---|---|
| Coagulopathy | The safety and efficacy of IV rtPA for acute stroke patients with platelets <100,000/mm$^3$, INR >1.7, aPTT >40 s, or PT >15 s are unknown, and IV rtPA should not be administered. (COR III: Harm; LOE C-EO)<br><br>(In patients without history of thrombocytopenia, IV rtPA can be initiated before availability of platelet count but should be discontinued if platelet count is <100,000/mm$^3$. In patients without recent use of OACs or heparin, IV rtPA can be initiated before availability of coagulation test results but should be discontinued if INR is >1.7 or PT is abnormally elevated by local lab standards.) |
| LMWH | IV rtPA should not be administered to patients who have received a full treatment dose of LMWH within the previous 24 h. (COR III: Harm; LOE B-NR) |

Abbreviations: AC, anticoagulants; AIS, acute ischemic stroke; aPTT, activated partial thromboplastin time; BP, blood pressure; CMB, cerebral microbleed; COR, class of recommendation; CT, computed tomography; DW-MRI, diffusion-weighted magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery; GI, gastrointestinal; ICH, intracerebral hemorrhage; INR, international normalized ratio; IV, intravenous; LMWH, low-molecular-weight heparin; LOE, level of evidence; MCA, middle cerebral artery; MI, myocardial infarction; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NCCT, noncontrast computed tomography; NIHSS, National Institutes of Health Stroke Scale; OAC, oral anticoagulant; PT, prothromboplastin time; sICH, symptomatic intracerebral hemorrhage; and STEMI, ST-segment–elevation myocardial infarction.

## CLASS (STRENGTH) OF RECOMMENDATION

**CLASS I (STRONG)** — Benefit >>> Risk

Suggested phrases for writing recommendations:
- Is recommended
- Is indicated/useful/effective/beneficial
- Should be performed/administered/other
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is recommended/indicated in preference to treatment B
  - Treatment A should be chosen over treatment B

**CLASS IIa (MODERATE)** — Benefit >> Risk

Suggested phrases for writing recommendations:
- Is reasonable
- Can be useful/effective/beneficial
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is probably recommended/indicated in preference to treatment B
  - It is reasonable to choose treatment A over treatment B

**CLASS IIb (WEAK)** — Benefit ≥ Risk

Suggested phrases for writing recommendations:
- May/might be reasonable
- May/might be considered
- Usefulness/effectiveness is unknown/unclear/uncertain or not well established

**CLASS III: No Benefit (MODERATE)** — Benefit = Risk
*(Generally, LOE A or B use only)*

Suggested phrases for writing recommendations:
- Is not recommended
- Is not indicated/useful/effective/beneficial
- Should not be performed/administered/other

**CLASS III: Harm (STRONG)** — Risk > Benefit

Suggested phrases for writing recommendations:
- Potentially harmful
- Causes harm
- Associated with excess morbidity/mortality
- Should not be performed/administered/other

## LEVEL (QUALITY) OF EVIDENCE‡

**LEVEL A**
- High-quality evidence‡ from more than 1 RCT
- Meta-analyses of high-quality RCTs
- One or more RCTs corroborated by high-quality registry studies

**LEVEL B-R (Randomized)**
- Moderate-quality evidence‡ from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs

**LEVEL B-NR (Nonrandomized)**
- Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies
- Meta-analyses of such studies

**LEVEL C-LD (Limited Data)**
- Randomized or nonrandomized observational or registry studies with limitations of design or execution
- Meta-analyses of such studies
- Physiological or mechanistic studies in human subjects

**LEVEL C-EO (Expert Opinion)**

Consensus of expert opinion based on clinical experience

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR I and IIa; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

## References

Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association [published correction appears in Stroke. 2019 Dec;50(12):e440-e441]. *Stroke*. 2019;50(12):e344-e418. doi: 10.1161/STR.0000000000000211 **[Clinical Practice Guideline, Level of Evidence A]**