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Thrombolysis in Acute Ischemic Stroke

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AHA/ASA Guideline

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

Endorsed by the Society for Academic Emergency Medicine and The Neurocritical Care Society

Reviewed for evidence-based integrity and endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons.

Class of Recommendation (COR)

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 of Evidence (LOE)

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.

Inclusion and Exclusion Criteria

2.2.2. IV Alteplase Eligibility	COR	LOE	New, Revised, or Unchanged
1. Administration of IV alteplase in eligible patients <u>without first obtaining MRI to exclude cerebral microbleeds (CMBs)</u> is recommended.	I	B-NR	New recommendation.
CMBs are common in patients receiving IV alteplase, occurring in 15% to 27%.^{89–94} Such patients were undoubtedly included in the pivotal NINDS and ECASS III trials that established the benefits of IV alteplase treatment.^{48,49} Two meta-analyses of the association of baseline CMBs and the risk of sICH after IV alteplase reported that sICH is more common in patients with baseline CMBs, whereas 2 other meta-analyses and 1 multicenter study did not.^{89–93} In 2 studies using ECASS II sICH criteria, the rates in patients with CMBs were 5.8% and 6.5% compared with 5.3% in ECASS III.^{49,90,91} One study analyzing the risk of sICH in patients with CMBs detected after IV alteplase treatment reported sICH of 5% using the NINDS criteria compared with 6.4% in the NINDS tPA trials.^{48,94} The risk of sICH in <u>patients with >10 CMBs (30%–47%)</u> is consistently reported as significantly greater than in those with no CMBs (1%–4.4%). However, these data are based on <50 patients, constituting <2% of these series.^{90,91,93,94} No RCTs of IV alteplase in AIS with baseline MRI to identify CMBs have been conducted, so no determination of the effect of baseline CMB on the treatment effect of alteplase with CMB is available. In the absence of direct evidence that IV alteplase provides no benefit or produces harm in eligible patients with CMBs, withholding treatment on the basis of the presence of CMBs could lead to the exclusion of patients who would benefit from treatment.			See Table XXI in online Data Supplement 1 .

2.2.2. IV Alteplase Eligibility (Continued)	COR	LOE	New, Revised, or Unchanged
2. In patients eligible for IV alteplase, because benefit of therapy is time dependent, treatment should be initiated as quickly as possible and <u>not delayed for additional multimodal neuroimaging, such as CT and MRI perfusion imaging.</u>	I	B-NR	New recommendation.
NCCT was the only neuroimaging modality used in the NINDS rt-PA trial and in ECASS III and is therefore sufficient neuroimaging for decisions about IV alteplase in most patients. ^{48,49} Multimodal CT and MRI, including diffusion and perfusion imaging, are not necessary when the diagnosis of ischemic stroke is very likely, and their performance may delay time-sensitive administration of IV alteplase. In some cases, particularly when there is substantial diagnostic uncertainty, advanced imaging may be beneficial.			See Table XX in online Data Supplement 1 .
3. In patients with AIS who awake with stroke symptoms or <u>have unclear time of onset > 4.5 hours from last known well or at baseline state, MRI to identify diffusion-positive FLAIR-negative lesions</u> can be useful for selecting those who can benefit from IV alteplase administration within 4.5 hours of stroke symptom recognition.	IIa	B-R	New recommendation.

2.2.3. Mechanical Thrombectomy Eligibility–Vessel Imaging	COR	LOE	New, Revised, or Unchanged
1. For patients who otherwise meet criteria for mechanical thrombectomy, <u>noninvasive vessel imaging of the intracranial arteries</u> is recommended during the initial imaging evaluation.	I	A	Recommendation reworded for clarity from 2015 Endovascular. COR and LOE unchanged. See Table XCV in online Data Supplement 1 for original wording.
2. For patients with suspected LVO who have not had noninvasive vessel imaging as part of their initial imaging assessment for stroke, <u>noninvasive vessel imaging should then be obtained as quickly as possible</u> (eg, during alteplase infusion if feasible).	I	A	Recommendation revised from 2015 Endovascular. COR and LOE unchanged.
3. In patients with suspected intracranial LVO and <u>no history of renal impairment</u> , who otherwise meet criteria for mechanical thrombectomy, it is reasonable to proceed with <u>CTA if indicated before obtaining a serum creatinine concentration</u> .	IIa	B-NR	New recommendation.
4. In patients who are potential candidates for mechanical thrombectomy, <u>imaging of the extracranial carotid and vertebral arteries. in addition to the intracranial circulation</u> , may be reasonable to provide useful information on patient eligibility and endovascular procedural planning.	IIb	C-EO	New recommendation.

2.2.3. Mechanical Thrombectomy Eligibility–Vessel Imaging (Continued)	COR	LOE	New, Revised, or Unchanged
5. It may be reasonable to <u>incorporate collateral flow status</u> into clinical decision-making in some candidates to determine eligibility for mechanical thrombectomy.	IIb	C-LD	Recommendation revised from 2015 Endovascular.

2.2.4. Mechanical Thrombectomy Eligibility–Multimodal Imaging	COR	LOE	New, Revised, or Unchanged
1. When selecting patients with <u>AIS within 6 to 24 hours of last known normal</u> who have LVO in the anterior circulation, <u>obtaining CTP or DW-MRI</u> , with or without MRI perfusion, is recommended to aid in patient selection for mechanical thrombectomy, but only when patients meet other eligibility criteria from one of the RCTs that showed benefit from mechanical thrombectomy in this extended time window.	I	A	New recommendation.
2. When evaluating patients with <u>AIS within 6 hours of last known normal</u> with LVO and an Alberta Stroke Program Early Computed Tomography Score (ASPECTS) of <u>≥6</u> , <u>selection for mechanical thrombectomy based on CT and CTA or MRI and MRA</u> is recommended in preference to performance of <u>additional imaging</u> such as perfusion studies.	I	B-NR	New recommendation.

3.5. IV Alteplase

3.5.1. General Principles	COR	LOE	New, Revised, or Unchanged
1. In patients eligible for IV alteplase, benefit of therapy is time dependent, and <u>treatment should be initiated as quickly as possible.</u>	I	A	Recommendation reworded for clarity from 2013 AIS Guidelines. COR and LOE unchanged. See Table XCV in online Data Supplement 1 for original wording.
2. In patients undergoing fibrinolytic therapy, physicians should be prepared to <u>treat potential emergent adverse effects, including bleeding complications and angioedema that may cause partial airway obstruction.</u>	I	B-NR	Recommendation reworded for clarity from 2013 AIS Guidelines. COR unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording.
See Table 6 for options for management of symptomatic intracranial bleeding occurring within 24 hours after administration of IV alteplase for treatment of AIS and Table 7 for options for management of orolingual angioedema associated with IV alteplase administration for AIS.			
3. <u>The potential risks should be discussed during IV alteplase eligibility deliberation and weighed against the anticipated benefits during decision-making.</u>	I	C-EO	Recommendation and COR unchanged from 2015 IV Alteplase. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.

3.5. IV Alteplase

4. Treating clinicians should be aware that hypoglycemia and hyperglycemia may mimic acute stroke presentations and determine blood glucose levels before IV alteplase initiation. <u>IV alteplase is not indicated for nonvascular conditions.</u>	III: No Benefit	B-NR	Recommendation reworded for clarity from 2015 IV Alteplase. COR and LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording.
5. Because time from onset of symptoms to treatment has such a powerful impact on outcomes, <u>treatment with IV alteplase should not be delayed to monitor for further improvement.</u>	III: Harm	C-EO	Recommendation wording modified from 2015 IV Alteplase to match COR III stratifications and reworded for clarity. COR and LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording.

3.5.2. Time Windows	COR	LOE	New, Revised, or Unchanged
1. IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 minutes with initial 10% of dose given as bolus over 1 minute) is recommended for selected patients who can be treated <u>within 3 hours of ischemic stroke symptom onset</u> or patient last known well or at baseline state. Physicians should review the criteria outlined in Table 8 to determine patient eligibility.	I	A	Recommendation reworded for clarity from 2013 AIS Guidelines. COR and LOE unchanged. See Table XCV in online Data Supplement 1 for original wording.
2. IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 minutes with initial 10% of dose given as bolus over 1 minute) is also recommended for selected patients who can be treated <u>within 3 and 4.5 hours of ischemic stroke symptom onset</u> or patient last known well or at baseline state. Physicians should review the criteria outlined in Table 8 to determine patient eligibility.	I	B-R	Recommendation reworded for clarity from 2013 AIS Guidelines. COR unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording.
3. IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 minutes with initial 10% of dose given as bolus over 1 minute) administered within 4.5 hours of stroke symptom recognition can be beneficial in patients with AIS who awake with stroke symptoms or have <u>unclear time of onset >4.5 hours</u> from last known well or at baseline state and who have a DW-MRI lesion <u>smaller than one-third of the MCA territory</u> and <u>no visible signal change on FLAIR</u> .	IIa	B-R	New recommendation.

3.5.3. Mild Stroke	COR	LOE	New, Revised, or Unchanged
1. For otherwise eligible patients with mild but disabling stroke symptoms, IV alteplase is recommended for patients who can be treated within 3 hours of ischemic stroke symptom onset or patient last known well or at baseline state.	I	B-R	Recommendation revised from 2015 IV Alteplase. COR and LOE added to conform with ACC/AHA 2015 Recommendation Classification System.
2. For otherwise eligible patients with mild disabling stroke symptoms, IV alteplase may be reasonable for patients who can be treated within 3 and 4.5 hours of ischemic stroke symptom onset or patient last known well or at baseline state.	IIb	B-NR	New recommendation.
3. For otherwise eligible patients with mild nondisabling stroke symptoms (NIHSS score 0–5), IV alteplase is not recommended for patients who could be treated within 3 hours of ischemic stroke symptom onset or patient last known well or at baseline state.	III: No Benefit	B-R	New recommendation.
4. For otherwise eligible patients with mild non-disabling stroke symptoms (NIHSS 0–5), IV alteplase is not recommended for patients who could be treated within 3 and 4.5 hours of ischemic stroke symptom onset or patient last known well or at baseline state.	III: No Benefit	C-LD	New recommendation.

3.5.4. Other Specific Circumstances	COR	LOE	New, Revised, or Unchanged
1. IV alteplase for adults presenting with an AIS with known <u>sickle cell disease</u> can be beneficial.	Ila	B-NR	New recommendation.
A case-control analysis using the population from the AHA GWTG-Stroke registry, including 832 cases with sickle cell disease (all adults) and 3328 age-, sex-, and race-matched controls without sickle cell disease with similar severity of neurological deficits at presentation, showed that sickle cell disease did not have a significant impact on the safety or the outcome at discharge of treatment with IV alteplase. ¹⁶⁹			See Table XXXVII in online Data Supplement 1 .
2. In patients with a <u>hyperdense MCA sign</u>, IV alteplase can be beneficial.	Ila	B-NR	New recommendation.
Analyses of data from RCTs of IV alteplase for AIS have shown no statistically significant deleterious interaction on clinical outcomes between alteplase treatment and the hyperdense MCA sign on baseline CT. In the NINDS rt-PA trial, there was no interaction between hyperdense MCA sign and treatment for outcomes at 3 months measured by any of the 4 clinical scales (mRS score 0–1, NIHSS score 0–1, Barthel Index score ≥95, Glasgow Outcome Scale score 0–1) or for death. ¹⁷⁰ In IST-3, no significant interaction of the hyperdense MCA sign with benefit of alteplase measured by the Oxford Handicap Score at 6 months was observed. ^{171,172}			See Table XXXVIII in online Data Supplement 1 .

3.5.5. Bleeding Risk	COR	LOE	New, Revised, or Unchanged
1. Given the extremely low risk of unsuspected abnormal platelet counts or coagulation studies in a population, it is reasonable that <u>urgent IV alteplase treatment not be delayed while waiting for hematologic or coagulation testing if there is no reason to suspect an abnormal test.</u>	IIa	B-NR	Recommendation and COR unchanged from 2015 IV Alteplase. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
2. In otherwise eligible patients who have <u>previously had a small number (1–10) of CMBs demonstrated on MRI</u> , administration of IV alteplase is reasonable.	IIa	B-NR	New recommendation.
3. In otherwise eligible patients who have <u>previously had a high burden of CMBs (>10) demonstrated on MRI</u> , treatment with IV alteplase 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.	IIb	B-NR	New recommendation.
4. <u>The efficacy of the IV glycoprotein IIb/IIIa inhibitors tirofiban and eptifibatide coadministered with IV alteplase is not well established.</u>	IIb	B-R	Recommendation revised from 2013 AIS Guidelines.

3.5.5. Bleeding Risk (Continued)	COR	LOE	New, Revised, or Unchanged
<u>5. Abciximab should not be administered concurrently with IV alteplase.</u>	III: Harm	B-R	Recommendation reworded for clarity from 2015 IV Alteplase. COR and LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording.
<u>6. IV aspirin should not be administered within 90 minutes after the start of IV alteplase.</u>	III: Harm	B-R	New recommendation.
<u>7. IV alteplase should not be administered to patients who have received a full treatment dose of low-molecular-weight heparin (LMWH) within the previous 24 hours.</u>	III: Harm	B-NR	Recommendation reworded for clarity from 2015 IV Alteplase. COR and LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording.

Table 8. Eligibility Recommendations for IV Alteplase in Patients With AIS

Indications (COR I)	
Within 3 h*	<u>IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 min with initial 10% of dose given as bolus over 1 min)</u> 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–Age	For otherwise medically eligible patients ≥ 18 y of age, IV alteplase administration within 3 h is equally recommended for <u>patients ≤ 80 and >80 y of age.</u> † (COR I; LOE A)
Within 3 h–Severe stroke	For severe stroke, IV alteplase is indicated within 3 h from symptom onset of ischemic stroke. Despite increased risk of hemorrhagic transformation, there is still proven clinical <u>benefit for patients with severe stroke symptoms.</u> † (COR I; LOE A)
Within 3 h–Mild disabling stroke	For otherwise eligible patients with mild but disabling stroke symptoms, IV alteplase 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*	<u>IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 min with initial 10% of dose given as bolus over 1 min)</u> 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–Age	IV alteplase treatment in the 3- to 4.5-h time window is recommended for those patients <u>≤ 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.</u> † (COR I; LOE B–R)§

Table 8. Eligibility Recommendations for IV Alteplase in Patients With AIS

Indications (COR I)	
Urgency	Treatment should be initiated <u>as quickly as possible</u> within the above-listed time frames because time to treatment is strongly associated with outcomes.† (COR I; LOE A)
BP	IV alteplase is recommended in patients with BP <u><185/110 mm Hg</u> 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 alteplase.† (COR I; LOE B-NR)§
Blood glucose	IV alteplase is recommended in otherwise eligible patients with initial glucose levels <u>>50 mg/dL</u> .† (COR I; LOE A)
CT	IV alteplase administration is recommended in <u>the setting of early ischemic changes on NCCT of mild to moderate extent (other than frank hypodensity)</u> .† (COR I; LOE A)
Prior antiplatelet therapy	IV alteplase is recommended for patients taking <u>antiplatelet drug monotherapy</u> before stroke on the basis of evidence that the benefit of alteplase outweighs a possible small increased risk of sICH.† (COR I; LOE A)
	IV alteplase is recommended for patients taking <u>antiplatelet drug combination therapy</u> (eg, aspirin and clopidogrel) before stroke on the basis of evidence that the benefit of alteplase outweighs a probable increased risk of sICH.† (COR I; LOE B-NR)§
End-stage renal disease	In patients with <u>end-stage renal disease on hemodialysis and normal aPTT</u> , IV alteplase 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 alteplase for patients with AIS (COR IIa)	And (COR IIb)
3 to 4.5 h–Age	For <u>patients >80 y of age presenting in the 3- to 4.5-h window</u> , IV alteplase 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 alteplase may be as effective as treatment in the 0- to 3-h window and may be a <u>reasonable option</u> .† (COR IIb; LOE B-NR)§
3 to 4.5 h–Severe stroke	The benefit of IV alteplase between 3 and 4.5 h from symptom onset for patients with very severe stroke symptoms (NIHSS score <u>>25</u>) is <u>uncertain</u> .† (COR IIb; LOE C-LD)§
3 to 4.5 h–Mild disabling stroke	For otherwise eligible patients with mild disabling stroke, IV alteplase 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 <u>at baseline state</u> . (COR IIb; LOE B-NR)‡
Wake-up and unknown time of onset	IV alteplase (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 <u>DW-MRI lesion smaller than one-third of the MCA territory and no visible signal change on FLAIR</u> . (COR IIa; LOE B-R)‡
Preexisting disability	Preexisting disability does not seem to independently increase the risk of sICH after IV alteplase, but it may be associated with less neurological improvement and higher mortality. Therapy with IV alteplase for acute stroke patients with preexisting disability (mRS score ≥ 2) may be reasonable, but decisions should take into account <u>relevant factors, including quality of life, social support, place of residence, need for a caregiver, patients' and families' preferences, and goals of care</u> .† (COR IIb; LOE B-NR)§

Additional recommendations for treatment with IV alteplase 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 alteplase, but it may be associated with less neurological improvement and higher mortality. Therapy with IV alteplase 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)§
	Patients with preexisting dementia may benefit from IV alteplase. Individual considerations such as life expectancy and premorbid level of function are important to determine whether alteplase may offer a clinically meaningful benefit.† (COR IIb; LOE B-NR)§
Early improvement	IV alteplase 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 alteplase 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	Treatment with IV alteplase 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. (Recommendation modified from 2015 IV Alteplase to conform to text of 2015 IV Alteplase. [COR IIb; LOE C-LD])§
Coagulopathy	IV alteplase 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 alteplase for acute stroke patients with a clinical history of potential bleeding diathesis or coagulopathy are unknown. IV alteplase may be considered on a case-by-case basis.† (COR IIb; LOE C-EO)§

Additional recommendations for treatment with IV alteplase for patients with AIS (COR IIa)

And (COR IIb)

Dural puncture	IV alteplase may be considered for patients who present with AIS, even in instances when they may have undergone a lumbar dural <u>puncture in the preceding 7 d.</u> † (COR IIb; LOE C-EO)§
Arterial puncture	The safety and efficacy of administering IV alteplase to acute stroke patients who have had an arterial puncture of a noncompressible blood <u>vessel in the 7 d preceding stroke</u> symptoms are uncertain.† (COR IIb; LOE C-LD)§
Recent major trauma	In AIS patients with <u>recent major trauma (within 14 d) not involving the head</u> , IV alteplase 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. (Recommendation modified from 2015 IV Alteplase to specify that it does not apply to head trauma. [COR IIb; LOE C-LD])§
Recent major surgery	Use of IV alteplase in carefully selected patients presenting with AIS who have undergone a major surgery in the preceding <u>14 d may be considered, but the potential increased risk of surgical-site hemorrhage</u> should be weighed against the anticipated benefits of reduced stroke related neurological deficits.† (COR IIb; LOE C-LD)§
GI and genitourinary bleeding	Reported literature details a low bleeding risk with IV alteplase administration in the <u>setting of past GI/genitourinary bleeding</u> . Administration of IV alteplase in this patient population may be reasonable.† (COR IIb; LOE C-LD)§ (Note: Alteplase administration within 21 d of a GI bleeding event is not recommended; see Contraindications.)

Additional recommendations for treatment with IV alteplase for patients with AIS (COR IIa)	And (COR IIb)
Menstruation	IV alteplase is probably indicated in women who are menstruating who present with <u>AIS and do not have a history of menorrhagia</u> . However, women should be warned that alteplase treatment could increase the degree of menstrual flow.† (COR IIa; LOE C-EO)§
	When there is a history of recent or active vaginal bleeding causing <u>clinically significant anemia</u> , then <u>emergency consultation with a gynecologist is probably indicated</u> before a decision about IV alteplase is made.† (COR IIa; LOE C-EO)§
	Because the potential benefits of IV alteplase probably outweigh the risks of serious bleeding in patients with recent or active history of menorrhagia <u>without clinically significant anemia or hypotension</u> , IV alteplase administration may be considered.† (COR IIb; LOE C-LD)§
Extracranial cervical dissections	IV alteplase in AIS known or suspected to be associated with extracranial cervical arterial dissection is reasonably safe <u>within 4.5 h and probably recommended</u> .† (COR IIa; LOE C-LD)§
Intracranial arterial dissection	IV alteplase usefulness and hemorrhagic risk in AIS known or suspected to be associated with intracranial arterial dissection remain unknown, uncertain and <u>not well established</u> .† (COR IIb; LOE C-LD)§
Unruptured intracranial aneurysm	For patients presenting with AIS who are known to harbor a <u>small or moderate-sized (<10 mm) unruptured and unsecured intracranial aneurysm</u> , administration of IV alteplase is reasonable and probably recommended.† (COR IIa; LOE C-LD)§
	Usefulness and risk of IV alteplase in patients with AIS who <u>harbor a giant unruptured and unsecured intracranial aneurysm</u> are not well established.† (COR IIb; LOE C-LD)§

Additional recommendations for treatment with IV alteplase for patients with AIS (COR IIa)

And (COR IIb)

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 alteplase are not well established.† (COR IIb; LOE C-LD)§
	Because of the increased risk of ICH in this population of patients, IV alteplase may be considered in patients with stroke with severe <u>neurological deficits and a high likelihood of morbidity and mortality to outweigh the anticipated risk of ICH.</u> † (COR IIb; LOE C-LD)§
CMBs	In otherwise eligible patients who have previously had a <u>small number (1–10) of CMBs</u> demonstrated on MRI, administration of IV alteplase is reasonable. (COR IIa; Level B-NR)‡
	In otherwise eligible patients who have previously had a high burden of <u>CMBs (>10)</u> demonstrated on MRI, treatment with IV alteplase 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, eptifibatide	The efficacy of the IV glycoprotein IIb/IIIa inhibitors tirofiban and eptifibatide coadministered with IV alteplase is not well established. (COR IIb; Level B-NR)‡
Extra-axial intracranial neoplasms	IV alteplase treatment is probably recommended for patients with AIS who harbor an extra-axial intracranial neoplasm.† (COR IIa; LOE C-EO)§

Additional recommendations for treatment with IV alteplase for patients with AIS (COR IIa)	And (COR IIb)
Acute MI	For patients presenting with concurrent AIS and acute MI, treatment with <u>IV alteplase at the dose appropriate for cerebral ischemia, followed by percutaneous coronary angioplasty and stenting if indicated</u> , 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 alteplase is reasonable if the <u>recent MI was non-STEMI</u> .† (COR IIa; LOE C-LD)§
	For patients presenting with AIS and a history of recent MI in the past 3 mo, treating the ischemic stroke with IV alteplase is reasonable if the recent MI was a <u>STEMI involving the right or inferior myocardium</u> .† (COR IIa; LOE C-LD)§
	For patients presenting with AIS and a history of recent MI in the past 3 mo, treating the ischemic stroke with IV alteplase may be reasonable if the recent MI was a <u>STEMI involving the left anterior myocardium</u> .† (COR IIb; LOE C-LD)§
Acute pericarditis	For patients with major AIS likely to produce <u>severe disability and acute pericarditis</u> , treatment with IV alteplase may be reasonable† (COR IIb; LOE C-EO)§; urgent consultation with a cardiologist is recommended in this situation.
	For patients presenting with moderate AIS likely to produce mild disability and acute pericarditis, treatment with IV alteplase is of uncertain net benefit.† (COR IIb; LOE C-EO)§
Left atrial or ventricular thrombus	For patients with major AIS likely to produce <u>severe disability and known left atrial or ventricular thrombus</u> , treatment with IV alteplase may be reasonable.† (COR IIb; LOE C-LD)§
	For patients presenting with moderate AIS likely to produce mild disability and known left atrial or ventricular thrombus, treatment with IV alteplase is of uncertain net benefit.† (COR IIb; LOE C-LD)§

Additional recommendations for treatment with IV alteplase 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 alteplase may be reasonable.† (COR IIb; LOE C-LD)§
	For patients presenting with major AIS likely to produce severe disability and papillary fibroelastoma, treatment with IV alteplase may be reasonable.† (COR IIb; LOE C-LD)§
Procedural stroke	IV alteplase 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 alteplase in patients with current malignancy are not well established.† (COR IIb; LOE C-LD)§ Patients with systemic malignancy and reasonable (>6 mo) life expectancy may benefit from IV alteplase if other contraindications such as coagulation abnormalities, recent surgery, or systemic bleeding do not coexist.
Pregnancy	IV alteplase 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)§
	The safety and efficacy of IV alteplase in the early postpartum period (<14 d after delivery) have not been well established.† (COR IIb; LOE C-LD)§

Additional recommendations for treatment with IV alteplase for patients with AIS (COR IIa)

And (COR IIb)

Ophthalmological conditions	Use of IV alteplase in patients presenting with AIS who have a history of diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic conditions is reasonable to recommend, <u>but the potential increased risk of visual loss should be weighed against the anticipated benefits of reduced stroke-related neurological deficits.</u> † (COR IIa; LOE B-NR)§
Sickle cell disease	IV alteplase for adults presenting with an AIS <u>with known sickle cell disease can be beneficial.</u> (COR IIa; LOE B-NR)‡
Hyperdense MCA sign	In patients with a hyperdense MCA <u>sign, IV alteplase can be beneficial.</u> (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 alteplase is reasonable in instances of illicit drug use–associated <u>AIS in patients with no other exclusions.</u> † (COR IIa; LOE C-LD)§
Stroke mimics	The risk of symptomatic intracranial hemorrhage in the stroke mimic population is quite low; thus, starting IV alteplase 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 window—Mild nondisabling stroke	For otherwise eligible patients with mild nondisabling stroke (NIHSS score 0–5), IV alteplase 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—Mild nondisabling stroke	For otherwise eligible patients with mild nondisabling stroke (NIHSS score 0–5), IV alteplase 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 alteplase. However, administering IV alteplase to patients whose CT brain imaging exhibits extensive regions of clear hypoattenuation is not recommended. These patients have a poor prognosis despite IV alteplase, and severe hypoattenuation defined as <u>obvious hypodensity represents irreversible injury</u> .† (COR III: No Benefit; LOE A)‖
ICH	IV alteplase 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 alteplase 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 alteplase is contraindicated.† (COR III: Harm; LOE C-EO)§‖
Acute head trauma	Given the possibility of bleeding complications from the underlying severe head trauma, IV alteplase should not be administered in <u>posttraumatic infarction that occurs during the acute in-hospital phase</u> .† (COR III: Harm; LOE C-EO)§‖ (Recommendation wording modified to match COR III stratifications.)

Contraindications (COR III: No Benefit)

And (COR III: Harm)

Intracranial/intraspinal surgery within 3 mo	For patients with AIS and a history of intracranial/spinal surgery within the prior 3 mo, IV alteplase is potentially harmful.† (COR III: Harm; LOE C-EO)§
History of intracranial hemorrhage	IV alteplase administration in patients who have a history of intracranial hemorrhage is potentially harmful.† (COR III: Harm; LOE C-EO)§
Subarachnoid hemorrhage	IV alteplase 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 alteplase administration is potentially harmful.† (COR III: Harm; LOE C-EO)§
Coagulopathy	The safety and efficacy of IV alteplase for acute stroke patients with <u>platelets <100 000/mm³, INR >1.7, aPTT >40 s, or PT >15 s</u> are unknown, and IV alteplase should not be administered.† (COR III: Harm; LOE C-EO)§ (In patients without history of thrombocytopenia, treatment with IV alteplase 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, treatment with IV alteplase 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 laboratory standards.) (Recommendation wording modified to match COR III stratifications.)
LMWH	IV alteplase should not be administered to patients who have received a <u>full treatment dose of LMWH within the previous 24 h</u> .† (COR III: Harm; LOE B-NR)§‡ (Recommendation wording modified to match COR III stratifications.)

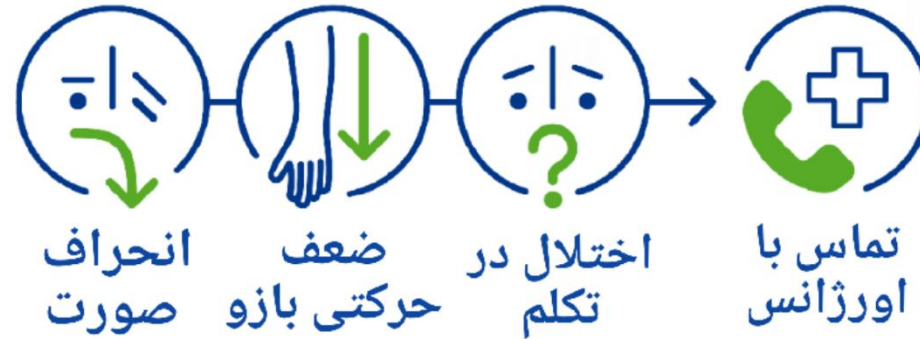
Contraindications (COR III: No Benefit)

And (COR III: Harm)

Thrombin inhibitors or factor Xa inhibitors	The use of IV alteplase in patients taking direct thrombin inhibitors or direct factor Xa inhibitors has not been firmly established but may be harmful.† (COR III: Harm; LOE C-EO)§ IV alteplase should not be administered to patients taking direct thrombin inhibitors or direct factor Xa inhibitors unless laboratory tests such as aPTT, INR, platelet count, ecarin clotting time, thrombin time, or appropriate direct factor Xa activity assays are normal or the patient has not received a dose of these agents for >48 h (assuming normal renal metabolizing function). (Alteplase could be considered when appropriate laboratory tests such as aPTT, INR, ecarin clotting time, thrombin time, or direct factor Xa activity assays are normal or when the patient has not taken a dose of these ACs for >48 h and renal function is normal.) (Recommendation wording modified to match COR III stratifications.)
Concomitant Abciximab	Abciximab should not be administered concurrently with IV alteplase. (COR III: Harm; LOE B-R)‡
Concomitant IV aspirin	IV aspirin should not be administered within 90 min after the start of IV alteplase. (COR III: Harm; LOE B-R)‡
Infective endocarditis	For patients with AIS and symptoms consistent with infective endocarditis, treatment with IV alteplase should not be administered because of the increased risk of intracranial hemorrhage.† (COR III: Harm; LOE C-LD)§ (Recommendation wording modified to match COR III stratifications.)
Aortic arch dissection	IV alteplase in AIS known or suspected to be associated with aortic arch dissection is potentially harmful and should not be administered.† (COR III: Harm; LOE C-EO)§ (Recommendation wording modified to match COR III stratifications.)
Intra-axial intracranial neoplasm	IV alteplase treatment for patients with AIS who harbor an intra-axial intracranial neoplasm is potentially harmful.† (COR III: Harm; LOE C-EO)§

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