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 treatment should be initiated as quickly as possible.	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 treat potential emergent adverse effects, including bleeding complications and angioedema that may cause partial airway obstruction.	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. The potential risks should be discussed during IV alteplase eligibility deliberation and weighed against the anticipated benefits during decision-making.	I	C-EO	Recommendation and COR unchanged from 2015 IV Alteplase. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
4. Treating clinicians should be aware that hypoglycemia and hyperglycemia may mimic acute stroke presentations and determine blood glucose levels before IV alteplase initiation. IV alteplase is not indicated for nonvascular conditions.	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, treatment with IV alteplase should not be delayed to monitor for further improvement.	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.

Table 5. Options to Treat Arterial Hypertension in Patients With AIS Who Are Candidates for Emergency Reperfusion Therapy*

COR IIb	LOE C-EO
Patient otherwise eligible for emergency reperfusion therapy except that BP is >185/110 mm Hg:	
Labetalol 10–20 mg IV over 1–2 min, may repeat 1 time; or	
Nicardipine 5 mg/h IV, titrate up by 2.5 mg/h every 5–15 min, maximum 15 mg/h; when desired BP reached, adjust to maintain proper BP limits; or	
Clevidipine 1–2 mg/h IV, titrate by doubling the dose every 2–5 min until desired BP reached; maximum 21 mg/h	
Other agents (eg, hydralazine, enalaprilat) may also be considered	
If BP is not maintained ≤185/110 mm Hg, do not administer alteplase	
Management of BP during and after alteplase or other emergency reperfusion therapy to maintain BP ≤180/105 mm Hg:	
Monitor BP every 15 min for 2 h from the start of alteplase therapy, then every 30 min for 6 h, and then every hour for 16 h	
If systolic BP >180–230 mm Hg or diastolic BP >105–120 mm Hg:	
Labetalol 10 mg IV followed by continuous IV infusion 2–8 mg/min; or	
Nicardipine 5 mg/h IV, titrate up to desired effect by 2.5 mg/h every 5–15 min, maximum 15 mg/h; or	
Clevidipine 1–2 mg/h IV, titrate by doubling the dose every 2–5 min until desired BP reached; maximum 21 mg/h	
If BP not controlled or diastolic BP >140 mm Hg, consider IV sodium nitroprusside	

AIS indicates acute ischemic stroke; BP, blood pressure; COR, class of recommendation; IV, intravenous; and LOE, Level of Evidence.

*Different treatment options may be appropriate in patients who have comorbid conditions that may benefit from rapid reductions in BP such as acute coronary event, acute heart failure, aortic dissection, or preeclampsia/eclampsia.

Data derived from Jauch et al.[1]

The following seem to be predictors of favorable outcome with IV thrombolytic therapy with alteplase for acute ischemic stroke: treatment within 90 minutes of symptom onset, normal baseline CT scan, milder baseline stroke severity, no history of DM, normal pretreatment blood glucose level, and normal pretreatment blood pressure.

The following seem to portend a less favorable outcome and/or increased risk for cerebral hemorrhage: extended area of low attenuation with mass effect or low attenuation on a third or more of the MCA territory on pretreatment CT scan; advanced age; prior head injury; DM; marked elevation of the blood pressure before, during, and after treatment; hypertension requiring post-randomization antihypertensive treatment; severe pretreatment neurological deficits; and protocol violations according to the NINDS study protocol

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 within 3 hours of ischemic stroke symptom onset 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.
The safety and efficacy of this treatment when administered within the first 3 hours after stroke onset are solidly supported by combined data from multiple RCTs[155–157] and confirmed by extensive community experience in many countries.[158] The eligibility criteria for IV alteplase have evolved over time as its usefulness and true risks have become clearer. A recent AHA statement provides a detailed discussion of this topic.[14] Eligibility recommendations for IV alteplase in patients with AIS are summarized in Table 8. The benefit of IV alteplase is well established for adult patients with disabling stroke symptoms regardless of age and stroke severity.[78,159] Because of this proven benefit and the need to expedite treatment, when a patient cannot provide consent (eg, aphasia, confusion) and a legally authorized representative is not immediately available to provide proxy consent, it is justified to proceed with IV alteplase in an otherwise eligible adult patient with a disabling AIS. In a recent trial, a lower dose of IV alteplase (0.6 mg/kg) was not shown to be noninferior to standard-dose IV alteplase for the reduction of death and disability at 90 days.[160]			See Table XX in online Data Supplement 1.

3.5.2. Time Windows (Continued)	COR	LOE	New, Revised, or Unchanged
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 within 3 and 4.5 hours of ischemic stroke symptom onset 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.
One trial (ECASS III) specifically evaluating the efficacy of IV alteplase within 3 and 4.5 hours after symptom onset[49] and pooled analysis of multiple trials testing IV alteplase within various time windows[155–157] support the efficacy of IV alteplase up to 4.5 hours after symptom onset. ECASS III excluded octogenarians, patients taking warfarin regardless of international normalized ratio, patients with combined history of diabetes mellitus and previous ischemic stroke, and patients with very severe strokes (NIHSS score >25) because of a perceived excessive risk of intracranial hemorrhage in those cases. However, careful analysis of available published data summarized in an AHA/American Stroke Association (ASA) scientific statement indicates that these exclusion criteria from the trial may not be justified in practice (Table 8).[14]			See Table XX in online Data Supplement 1.
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 unclear time of onset >4.5 hours 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.	IIa	B-R	New recommendation.
The WAKE-UP RCT randomized 503 patients with AIS who awoke with stroke or had unclear time of onset and could be treated with IV alteplase within 4.5 hours of stroke symptom recognition. Eligibility required MRI mismatch between abnormal signal on DW-MRI and no visible signal change on FLAIR. DW-MRI lesions larger than one-third of the territory of the MCA, NIHSS score >25, contraindication to treatment with alteplase, or planned thrombectomy were all exclusions. Ninety-four percent were wake-up strokes. Median NIHSS score was 6. Median time from last known well to symptom recognition was ≈7 hours and to alteplase administration slightly over 10 hours. The primary end point of an mRS score 0 to 1 at 90 days was achieved in 53.3% of the alteplase group and in 41.8% of the placebo group (P=0.02). Only 20% had LVO of the intracranial internal carotid or proximal middle cerebral arteries.[88]			See Table XIX in online Data Supplement 1.

The time window for IV thrombolytic therapy may in the future be extended further. A recent clinical trial of MRI-guided thrombolysis for stroke with unknown time of onset suggested that patients with MR—DWI positive, FLAIR negative lesions showed a favorable outcome in the alteplase-treated group as compared with a placebo group (53.3% vs. 41.8%; *P* = 0.02)(Thomalla et al., 2018). Furthermore a recent trial using CT perfusion or MR diffusion/perfusion imaging found good functional outcome in patients treated with alteplase up to 9 hours after symptom onset (35% excellent outcome with alteplase vs 29% for placebo) with adjusted risk ratio of 1.44 (95% CI 1.01-2.06) with a P value of 0.042 (MA, 2019)).

The standard alteplase dose in the United States and Europe is 0.9 mg/kg. In Asian populations, however, studies have suggested that a lower dose of 0.6 mg/kg of alteplase may be equally effective. This recommendation is somewhat controversial. The Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED) found that patients with lower-dose alteplase failed to achieve non-inferiority in the primary outcome of death or disability, though there was less symptomatic ICH in the low-dose alteplase group. The current Chinese Stroke Association guidelines recommend full-dose IV alteplase, with lower-dose alteplase as a consideration for patients deemed at high risk of hemorrhage (Class IIb, Evidence level C) (Dong et al., 2017) In Japan, however, the lower alteplase dose of 0.6 mg/kg is recommended for acute stroke patients

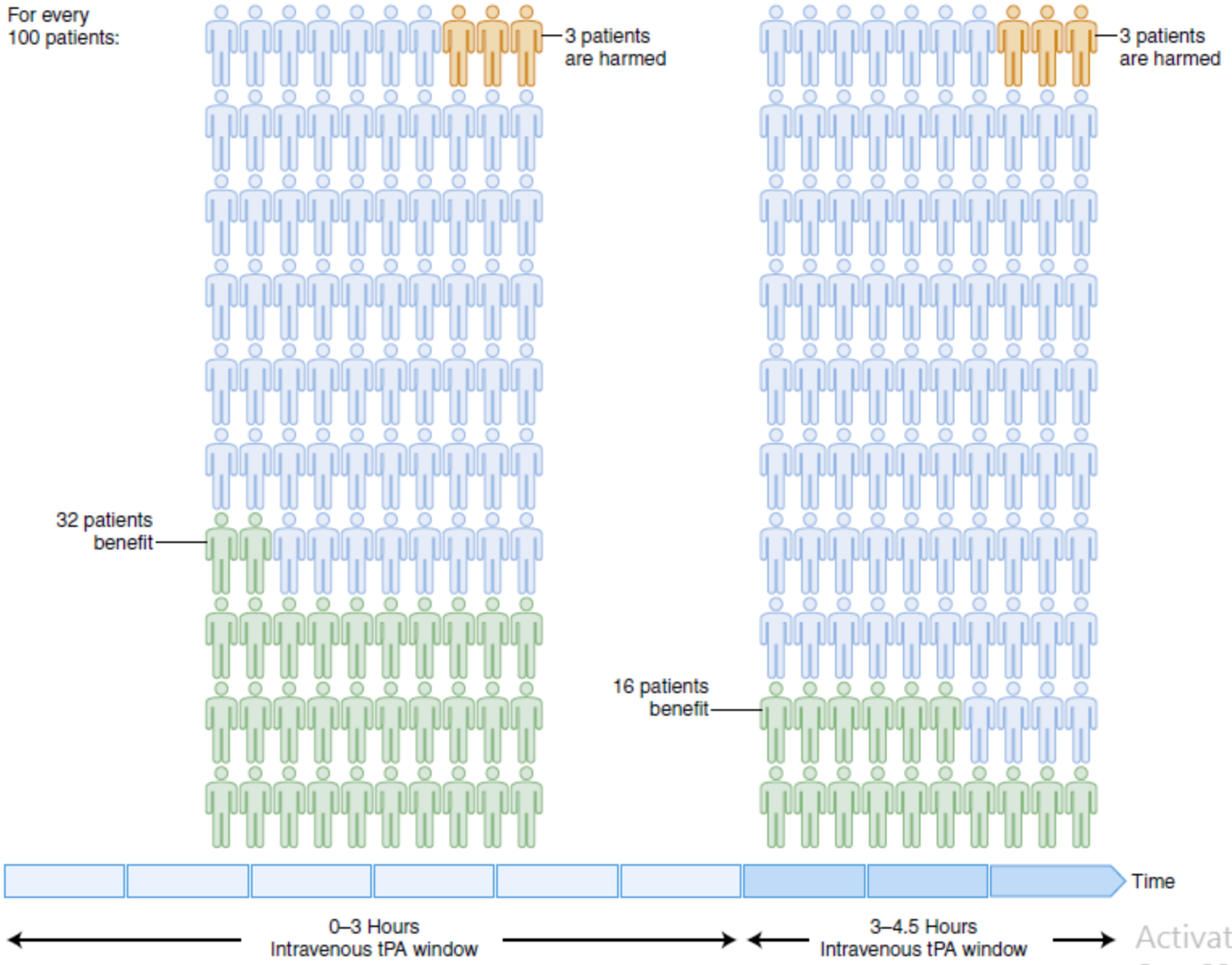

Fig. 65.29 Risk/benefit ratio of IV tissue plasminogen activator (*tPA*, alteplase) for acute ischemic stroke in the 0- to 3-hour and 3- to 4.5-hour windows. (Created and designed by Gabriel A. Biller.)

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.
Subgroup analyses of the NINDS rt-PA Trial and IST (International Stroke Trial)-3 with mild stroke defined in various ways have inconsistently shown a benefit for IV alteplase.[161–163] A meta-analysis of 9 trials of IV alteplase in AIS including subjects from the NINDS rt-PA trial and IST-3 showed benefit for patients with mild stroke defined as NIHSS score 0 to 4.[164] In ECASS III, there was no significant interaction of benefit (mRS score 0–1 at 90 days) or safety (sICH or death) with stroke severity when patients were categorized by baseline NIHSS score of 0 to 9, 10 to 19, and >20.[165] In SITS-ISTR (Safe Implementation of Treatments in Stroke–International Stroke Thrombolysis Registry), good functional outcomes (mRS score 0–1 at 90 days) and risk of sICH were similar or the same in mild stroke treated in 0 to 3 and 3 to 4.5 hours.[166] Similarly, in the AHA GWTG registry, good functional outcomes, mortality, and risk of sICH were the same in mild stroke treated in 0 to 3 and 3 to 4.5 hours.[167] These patients were not further categorized by whether their acute neurological deficits were disabling. The PRISMS RCT (A Study of the Safety and Efficacy of Activase [Alteplase] in Patients With Mild Stroke) evaluated IV alteplase in patients with mild (NIHSS score 0–5) AIS whose acute neurological deficits were judged to not interfere with activities of daily living or prevent return to work. There was no benefit of treatment within 3 hours of onset.[168]			See Tables XXXV and XXXVI in online Data Supplement 1.

3.5.4. Other Specific Circumstances	COR	LOE	New, Revised, or Unchanged
1. IV alteplase for adults presenting with an AIS with known sickle cell disease can be beneficial.	**IIa**	**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 hyperdense MCA sign, IV alteplase can be beneficial.	**IIa**	**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 urgent IV alteplase treatment not be delayed while waiting for hematologic or coagulation testing if there is no reason to suspect an abnormal test.	**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 previously had a small number (1–10) of CMBs demonstrated on MRI, administration of IV alteplase is reasonable.	**IIa**	**B-NR**	New recommendation.
3. In otherwise eligible patients who have previously had a high burden of CMBs (>10) 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.	**IIb**	**B-NR**	New recommendation.
CMBs are common in patients receiving IV alteplase, occurring in 15% to 27%.[89–94] 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. Two meta-analyses of the association of baseline CMBs on 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 rt-PA trials.[48,94] The risk of sICH in patients with >10 CMBs (30%–47%) 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] Meta-analysis of 4 studies that provide information on 3- to 6-month functional outcomes showed that the presence of CMBs was associated with worse outcomes after IV alteplase compared with patients without CMBs (OR, 1.58 [95% CI, 1.18–2.14]; P=0.002).[89] Thus, the presence of CMBs increases the risk of ICH and the chances of poor outcomes after IV alteplase, but it is unclear whether these negative effects fully negate the benefit of IV alteplase. It is also unknown whether the location and number of CMBs may differentially influence outcomes. These questions deserve further investigation.			See Table XXI in online Data Supplement 1.

4. The efficacy of the IV glycoprotein IIb/IIIa inhibitors tirofiban and eptifibatide coadministered with IV alteplase is not well established.	**IIb**	**B-R**	Recommendation revised from 2013 AIS Guidelines.
Single-arm studies of eptifibatide as adjunctive therapy to IV alteplase support ongoing RCTs to establish safety and efficacy.[173,174] Further clinical trials are needed.			See Table XXXIX in online Data Supplement 1.
5. Abciximab should not be administered concurrently with IV alteplase.	**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.
6. IV aspirin should not be administered within 90 minutes after the start of IV alteplase.	**III: Harm**	**B-R**	New recommendation.
The ARTIS trial (Antiplatelet Therapy in Combination with rt-PA Thrombolysis in Ischemic Stroke) compared the effects of very early addition (within 90 minutes) of 300 mg IV aspirin to alteplase with standard treatment with alteplase without IV aspirin.[175] The trial was terminated after 642 of the 800 targeted patients had been enrolled because IV aspirin was associated with an increased risk of symptomatic intracranial hemorrhage (4.3% versus 1.6% in the standard treatment group; RR, 2.78 [95% CI, 1.01–7.63]; *P*=0.04) and no difference in the rate of favorable functional outcome (mRS score 0–2) at 3 months (54.0% of patients in the aspirin group versus 57.2% of patients in the standard treatment group; RR, 0.94 [95% CI, 0.82–1.09]; *P*=0.42).			See Table XL in online Data Supplement 1.

3.5.5. Bleeding Risk (Continued)	COR	LOE	New, Revised, or Unchanged
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.	**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.
The recommendation refers to full treatment doses and not to prophylactic doses. The 2015 "Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke" stated, "Intravenous alteplase in patients who have received a dose of LMWH within the previous 24 hours is not recommended. This applies to both prophylactic doses and treatment doses (*COR III; Level of Evidence B*)."[14] This statement was updated in a subsequently published erratum to specify that the contraindication does not apply to prophylactic doses.			

3.5.6. Post-alteplase Treatment	COR	LOE	New, Revised, or Unchanged
1. BP should be maintained at <180/105 mm Hg for at least the first 24 hours after IV alteplase treatment.	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.
Main elements of postthrombolysis care are listed in Table 9. ENCHANTED (Enhanced Control of Hypertension and Thrombolysis Stroke Study) randomized 2196 alteplase-eligible patients with AIS and systolic BP (SBP) ≥150 mm Hg to receive intensive target SBP of 130 to 140 mm Hg within 1 hour versus guideline target SBP <180 mm Hg; 1081 were in the intensive group, and 1115 were in the guideline group.[176] Median time from stroke onset to randomization was 3.3 hours. Mean SBP in the intensive group was 144.3 mm Hg, and mean SBP in the guideline group was 149.8 mm Hg. Primary outcome mRS score at 90 days did not differ between the 2 groups. Although fewer patients in the intensive group had ICH, the number of patients with serious adverse events did not differ between the 2 groups. Although intensive BP lowering was observed to be safe, the observed reduction in ICH did not lead to improved clinical outcome compared with guideline treatment.			See Table XLI in online Data Supplement 1.
2. The risk of antithrombotic therapy (other than IV aspirin) within the first 24 hours after treatment with IV alteplase (with or without mechanical thrombectomy) is uncertain. Use might be considered in the presence of concomitant conditions for which such treatment given in the absence of IV alteplase is known to provide substantial benefit or withholding such treatment is known to cause substantial risk.	IIb	B-NR	New recommendation.
A retrospective analysis of consecutive ischemic stroke patients admitted to a single center in Seoul, South Korea, found no increased risk of hemorrhage with early initiation of antiplatelet or anticoagulant therapy (<24 hours) after IV alteplase or EVT compared with initiation >24 hours. However, this study may have been subject to selection bias, and the timing of the initiation of antiplatelet therapy or anticoagulation should be based on an individual level, balancing risk and benefit.[177]			See Table XLII in online Data Supplement 1.

Thrombolytic-related intracranial hemorrhages are usually large-volume lobar bleeds, often multiple, with blood/fluid levels; intraventricular and subarachnoid extension is not uncommon.

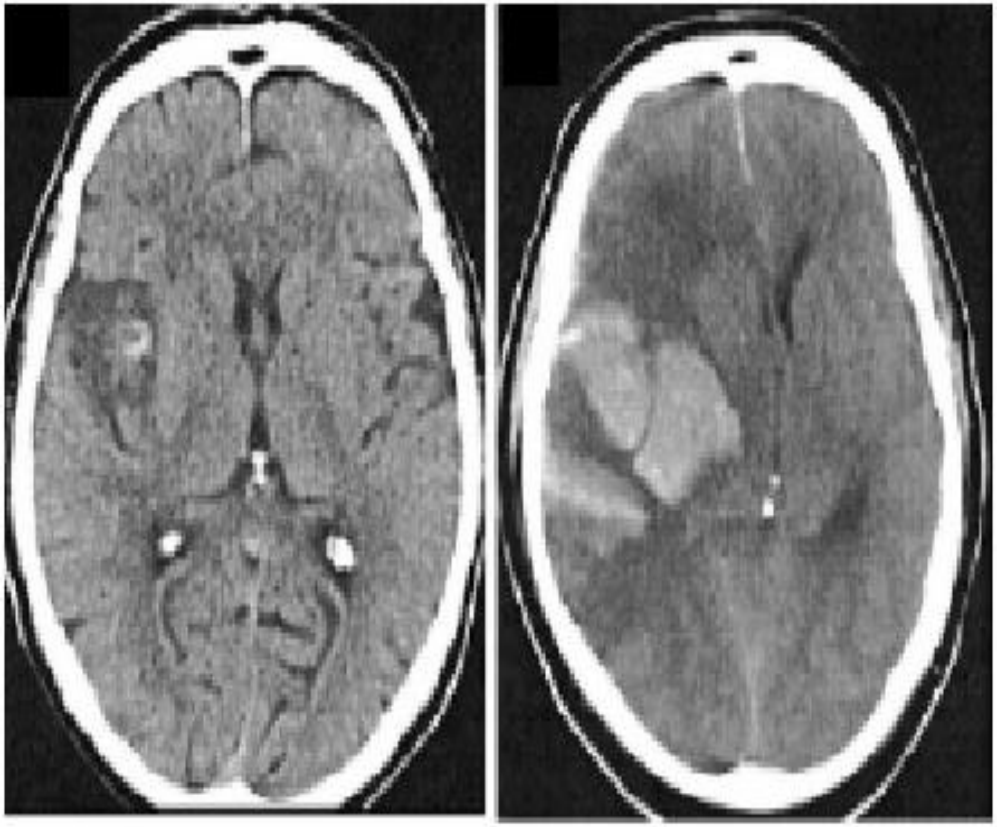

Table 6. Management of Symptomatic Intracranial Bleeding Occurring Within 24 Hours After Administration of IV Alteplase for Treatment of AIS

COR IIb	LOE C-EO
Stop alteplase infusion	
CBC, PT (INR), aPTT, fibrinogen level, and type and cross-match	
Emergent nonenhanced head CT	
Cryoprecipitate (includes factor VIII): 10 U infused over 10–30 min (onset in 1 h, peaks in 12 h); administer additional dose for fibrinogen level of <150 mg/dL	
Tranexamic acid 1000 mg IV infused over 10 min OR ε-aminocaproic acid 4–5 g over 1 h, followed by 1 g IV until bleeding is controlled (peak onset in 3 h) (Potential for benefit in all patients, but particularly when blood products are contraindicated or declined by patient/family or if cryoprecipitate is not available in a timely manner.)	
Hematology and neurosurgery consultations	
Supportive therapy, including BP management, ICP, CPP, MAP, temperature, and glucose control	

AIS indicates acute ischemic stroke; aPTT, activated partial thromboplastin time; BP, blood pressure; CBC, complete blood count; COR, class of recommendation; CPP, cerebral perfusion pressure; CT, computed tomography; ICP, intracranial pressure; INR, international normalized ratio; IV, intravenous; LOE, Level of Evidence; MAP, mean arterial pressure; and PT, prothrombin time.

Sources: Sloan et al,[138] Mahaffey et al,[139] Goldstein et al,[140] French et al,[141] Yaghi et al,[142–144] Stone et al,[145] and Frontera et al.[146]

Table 7. Management of Orolingual Angioedema Associated With IV Alteplase Administration for AIS

COR IIb	LOE C-EO
Maintain airway	
Endotracheal intubation may not be necessary if edema is limited to anterior tongue and lips.	
Edema involving larynx, palate, floor of mouth, or oropharynx with rapid progression (within 30 min) poses higher risk of requiring intubation.	
Awake fiberoptic intubation is optimal. Nasal-tracheal intubation may be required but poses risk of epistaxis after IV alteplase. Cricothyroidotomy is rarely needed and also problematic after IV alteplase.	
Discontinue IV alteplase infusion and hold ACE inhibitors	
Administer IV methylprednisolone 125 mg	
Administer IV diphenhydramine 50 mg	
Administer ranitidine 50 mg IV or famotidine 20 mg IV	
If there is further increase in angioedema, administer epinephrine (0.1%) 0.3 mL subcutaneously or by nebulizer 0.5 mL	
Icatibant, a selective bradykinin B_2 receptor antagonist, 3 mL (30 mg) subcutaneously in abdominal area; additional injection of 30 mg may be administered at intervals of 6 h not to exceed a total of 3 injections in 24 h; and plasma-derived C1 esterase inhibitor (20 IU/kg) has been successfully used in hereditary angioedema and ACE inhibitor-related angioedema	
Supportive care	

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

Indications (COR I)	
Within 3 h*	IV alteplase (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–Age	For otherwise medically eligible patients ≥18 y of age, IV alteplase 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 alteplase 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–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*	IV alteplase (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–Age	IV alteplase 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*)
BP	IV alteplase 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 alteplase.† (*COR I; LOE B-NR*)§
Blood glucose	IV alteplase is recommended in otherwise eligible patients with initial glucose levels >50 mg/dL.† (*COR I; LOE A*)
CT	IV alteplase 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*)

Table 8. Continued

Prior antiplatelet therapy	IV alteplase is recommended for patients taking antiplatelet drug monotherapy 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 antiplatelet drug combination therapy (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 end-stage renal disease on hemodialysis and normal aPTT, 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 patients >80 y of age presenting in the 3- to 4.5-h window, 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 reasonable option.† (*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 >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 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 at baseline state. (*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 DW-MRI lesion smaller than one-third of the MCA territory and no visible signal change on FLAIR. (*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 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*)§
Dural puncture	IV alteplase 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 alteplase 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 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 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*)§
GI and genitourinary bleeding	Reported literature details a low bleeding risk with IV alteplase administration in the setting of past GI/genitourinary bleeding. 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.)

(*Continued*)

Table 8. Continued

Menstruation	IV alteplase 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 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 clinically significant anemia, then emergency consultation with a gynecologist is probably indicated 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 without clinically significant anemia or hypotension, 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 within 4.5 h and probably recommended.† (*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 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 alteplase is reasonable and probably recommended.† (*COR IIa; LOE C-LD*)§
	Usefulness and risk of IV alteplase 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 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 neurological deficits and a high likelihood of morbidity and mortality to outweigh the anticipated risk of ICH.† (*COR IIb; LOE C-LD*)§
CMBs	In otherwise eligible patients who have previously had a small number (1–10) of CMBs 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 CMBs (>10) 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, epifibatide	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*)§
Acute MI	For patients presenting with concurrent AIS and acute MI, treatment with IV alteplase 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 alteplase is reasonable if the recent MI was non-STEMI.† (*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 STEMI involving the right or inferior myocardium.† (*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 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 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 severe disability and known left atrial or ventricular thrombus, 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*)§
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*)§

(*Continued*)

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*)§
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, 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 alteplase 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 alteplase 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 alteplase 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 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 obvious hypodensity represents irreversible injury.† (*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 posttraumatic infarction that occurs during the acute in-hospital phase.† (*COR III: Harm; LOE C-EO*)§‖ (Recommendation wording modified to match COR III stratifications.)
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 platelets <100 000/mm^3, INR >1.7, aPTT >40 s, or PT >15 s 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 full treatment dose of LMWH within the previous 24 h.† (*COR III: Harm; LOE B-NR*)§‡ (Recommendation wording modified to match COR III stratifications.)

Table 8. Continued

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*)§‖

Table 9. Treatment of AIS: IV Administration of Alteplase

Infuse 0.9 mg/kg (maximum dose 90 mg) over 60 min, with 10% of the dose given as a bolus over 1 min.
Admit the patient to an intensive care or stroke unit for monitoring.
If the patient develops severe headache, acute hypertension, nausea, or vomiting or has a worsening neurological examination, discontinue the infusion (if IV alteplase is being administered) and obtain emergency head CT scan.
Measure BP and perform neurological assessments every 15 min during and after IV alteplase infusion for 2 h, then every 30 min for 6 h, then hourly until 24 h after IV alteplase treatment.
Increase the frequency of BP measurements if SBP is >180 mm Hg or if DBP is >105 mm Hg; administer antihypertensive medications to maintain BP at or below these levels (Table 5).
Delay placement of nasogastric tubes, indwelling bladder catheters, or intra-arterial pressure catheters if the patient can be safely managed without them.
Obtain a follow-up CT or MRI scan at 24 h after IV alteplase before starting anticoagulants or antiplatelet agents.

AIS indicates acute ischemic stroke; BP, blood pressure; CT, computed tomography; DBP, diastolic blood pressure; IV, intravenous; MRI, magnetic resonance imaging; and SBP, systolic blood pressure.

3.6. Other IV Fibrinolytics and Sonothrombolysis

3.6. Other IV Fibrinolytics and Sonothrombolysis	COR	LOE	New, Revised, or Unchanged
1. It may be reasonable to choose tenecteplase (single IV bolus of 0.25-mg/kg, maximum 25 mg) over IV alteplase in patients without contraindications for IV fibrinolysis who are also eligible to undergo mechanical thrombectomy.	IIb	B-R	New recommendation.
IV tenecteplase (0.25 mg/kg bolus, maximum 25 mg) was compared with IV alteplase (usual dose of 0.9 mg/kg over 60 minutes, maximum 90 mg) in the EXTEND-IA TNK trial (Tenecteplase Versus Alteplase Before Endovascular Therapy for Ischemic Stroke).[178] This multicenter trial randomized 202 patients without previous severe disability and with documented occlusion of the internal carotid artery, proximal MCA (M1 or M2 segments), or basilar arteries presenting within 4.5 hours of symptom onset to receive 1 of these 2 fibrinolytic agents. Primary end point was reperfusion of >50% of the involved ischemic territory or an absence of retrievable thrombus at the time of the initial angiographic assessment. The trial was designed to test for noninferiority and, if noninferiority proven, for superiority. Secondary outcomes included the mRS score at 90 days. Median NIHSS score was 17. The primary end point was achieved by 22% of patients treated with tenecteplase versus 10% of those treated with alteplase (P=0.002 for noninferiority and 0.03 for superiority). In an analysis of secondary end points, tenecteplase resulted in better functional outcomes at 90 days on the basis of the ordinal shift analysis of the mRS score (common OR [cOR], 1.7 [95% CI, 1.0–2.8]; P=0.04) but less robustly for the proportion who achieved an mRS score of 0 to 1 (P=0.23) or 0 to 2 (P=0.06). sICH rates were 1% in both groups.			See Table XLIII in online Data Supplement 1.
2. Tenecteplase administered as a 0.4-mg/kg single IV bolus has not been proven to be superior or noninferior to alteplase but might be considered as an alternative to alteplase in patients with minor neurological impairment and no major intracranial occlusion.	IIb	B-R	New recommendation.
IV tenecteplase has been compared with IV alteplase up to 6 hours after stroke onset in 3 phase II and 1 phase III superiority trials; tenecteplase appears to be similarly safe, but it is unclear whether it is as effective as or more effective than alteplase.[179–182] In the largest trial of 1100 subjects, tenecteplase at a dose of 0.4 mg/kg failed to demonstrate superiority and had a safety and efficacy profile similar to that of alteplase in a stroke population composed predominantly of patients with minor neurological impairment (median NIHSS score, 4) and no major intracranial occlusion.[182] Tenecteplase is given as a single IV bolus as opposed to the 1-hour infusion of alteplase.			See Table XLIII in online Data Supplement 1.

infusion of alteplase.			
3. The administration of IV defibrinogenating agents or IV fibrinolytic agents other than alteplase and tenecteplase is not recommended.	**III: No Benefit**	**B-R**	Recommendation revised from 2013 AIS Guidelines.
Randomized placebo-controlled trials have not shown benefit from the administration of IV streptokinase within 6 hours or desmoteplase within 3 to 9 hours after stroke onset in patients with ischemic penumbra, large intracranial artery occlusion, or severe stenosis.[155,183–186]			See Table XLIII in online Data Supplement 1.
4. The use of sonothrombolysis as adjuvant therapy with IV fibrinolysis is not recommended.	**III: No Benefit**	**A**	New recommendation.
Since the publication of the 2013 AIS Guidelines, 2 RCTs of sonothrombolysis as adjuvant therapy for IV thrombolysis have shown no clinical benefit. NOR-SASS (Norwegian Sonothrombolysis in Acute Stroke Study) randomized 183 patients who had received either alteplase or tenecteplase for AIS within 4.5 hours of onset to either contrast-enhanced sonothrombolysis (93 patients) or sham (90 patients). Neurological improvement at 24 hours and functional outcome at 90 days were not statistically significantly different in the 2 groups, nor were the rates of sICH.[187] CLOTBUST-ER (Combined Lysis of Thrombus With Ultrasound and Systemic Tissue Plasminogen Activator [tPA] for Emergent Revascularization in Acute Ischemic Stroke) randomized 676 patients with AIS (NIHSS score ≥10) who received IV alteplase within 3 or 4.5 hours of symptom onset and randomly allocated to operator independent sonothrombolysis (335) or sham ultrasound (341).[188] Compared with the control arm, the neurological improvement, death, and serious adverse events in the intervention arm were not statistically different. At this time, there are no RCT data to support additional clinical benefit of sonothrombolysis as adjuvant therapy for IV fibrinolysis.			See Table XLIV in online Data Supplement 1.