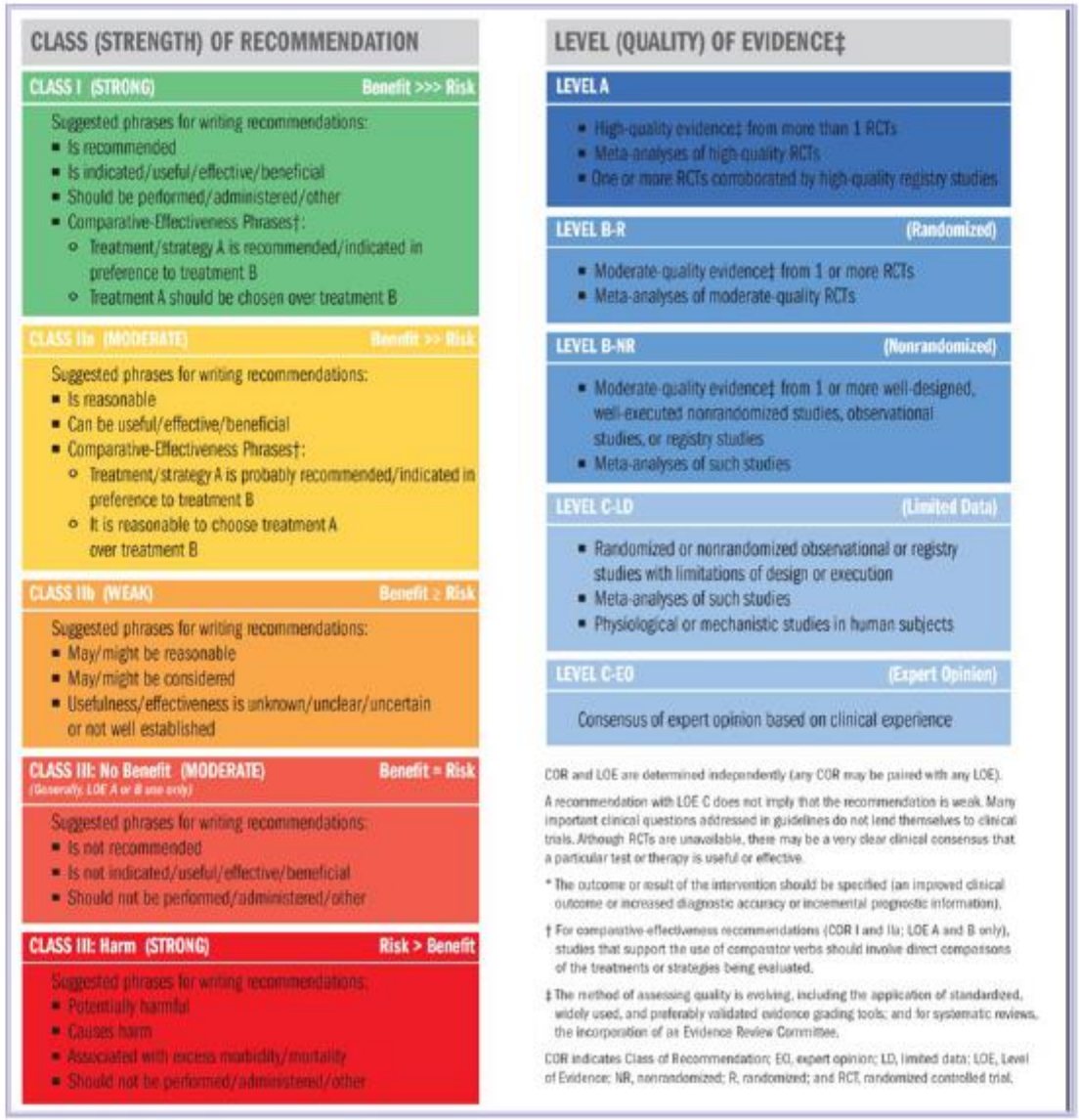
AHA/ASA GUIDELINES

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

Applying Classification of Recommendations and Level of Evidence



CLASS (STRENGTH) OF RECOMMENDATION

CLASS I (STRONG) — Benefit >>> Risk

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

CLASS IIa (MODERATE) — Benefit >> Risk

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

CLASS IIb (WEAK) — Benefit ≥ Risk

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

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

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

CLASS III: Harm (STRONG) — Risk > Benefit

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

LEVEL (QUALITY) OF EVIDENCE‡

LEVEL A
- High-quality evidence‡ from more than 1 RCTs
- 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.

American Heart Association.

General Supportive Care and Emergency Treatment

3.5 IV Alteplase

3.5.2 Time Windows

Recommendations	COR	LOE
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
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
3. IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 min 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 middle cerebral artery (MCA) territory and no visible signal change on FLAIR.	IIa	B-R

General Supportive Care and Emergency Treatment

3.6 Other IV Fibrinolytics and Sonothrombolysis

Recommendations	COR	LOE
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
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
3. The administration of IV defibrinogenating agents or IV fibrinolytic agents other than alteplase and tenecteplase is not recommended.	III: No Benefit	B-R
4. The use of sonothrombolysis as adjuvant therapy with IV fibrinolysis is not recommended.	III: No Benefit	A

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So, What Is Next?

- This recommendation made before EXTEND-IA TNK fully reported
- Community experiences being reported
- As Dr. Asimos mentioned, numerous trials underway
- What will happen after they report?

If Robustly POSITIVE

- AHA could issue a Practice / Science Advisory since new guidelines not in the near future
- Genentech may go for an indication if there is enough U.S. based data and it is *very* robust; may increase the price
- Community adoption will accelerate

Published in final edited form as:
Stroke. 2009 August ; 40(8): 2945–2948. doi:10.1161/STROKEAHA.109.192535.

Expansion of the Time Window for Treatment of Acute Ischemic Stroke With Intravenous Tissue Plasminogen Activator:

A Science Advisory From the American Heart Association/American Stroke Association

Gregory J. del Zoppo, MD, MS, FAHA [Chair], Jeffrey L. Saver, MD, FAHA, Edward C. Jauch, MD, MS, FAHA, and Harold P. Adams Jr, MD, FAHA on behalf of the American Heart Association Stroke Council

Comments and Opinions

Intravenous Recombinant Tissue-Type Plasminogen Activator in the Extended Time Window and the US Food and Drug Administration

Confused About the Time

Lawrence R. Wechsler, MD; Tudor G. Jovin, MD

If TEPID, NEUTRAL or NON-INFERIOR

- No guideline update since it is already IIb
- Genentech will do nothing
- Alteplase will remain SOC and tenecteplase adoption will be sporadic

If NEGATIVE

- AHA could issue a Practice / Science Advisory since new guidelines not in the near future if there is *major* harm
- Genentech will do nothing
- Community adoption will cease

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
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Data Table From 2019 Guidelines

ATTEST Huang X, et al. [179] 2015 25726502	**Aim**: Assess the efficacy and Safety of IV tenecteplase vs. alteplase within 4.5 h of stroke onset in a population not selected on the basis of advanced neuroimaging	**Inclusion criteria**: AIS <4.5 h; baseline CT, CTP, CTA **Exclusion criteria**: Standard criteria	**Intervention**: IV tenecteplase 0.25 mg/kg (n=52) **Comparator**: IV alteplase 0.9 mg/kg (n=52)	**1° end point**: Penumbral salvage: alteplase 68% (23%), tenecteplase 68% (28%), *P*=0.81 **Safety end point**: sICH: tenecteplase 6%, alteplase 8%, *P*=0.59	Recanalization: alteplase 74%, tenecteplase 66%, *P*=0.38	N/A	Not designed to prove imaging selection hypothesis; no difference in neurologic or radiologic outcomes
Parsons M, et al. [180] 2012 22435369	**Aim**: To compare IV tenecteplase vs. IV alteplase enhanced by imaging selection **Study type**: Phase IIB RCT **Size**: N=75	**Inclusion criteria**: AIS <6 h, CTA vessel occlusion **Exclusion criteria**: Standard alteplase exclusions	**Intervention**: IV tenecteplase 0.1 mg/kg (n=25); IV tenecteplase 0.25 mg/kg (n=25) **Comparator**: IV alteplase 0.9 mg/kg (n=25)	**1° end point**: Percent of perfusion lesion reperfused at 24 h: alteplase 55.4±38.7, tenecteplase 79.3±28.8, *P*=0.004; extent of clinical improvement (NIHSS) at 24 h: alteplase 3.0±6.3, tenecteplase 8.0±5.5, *P*<0.001 **Safety end point**: Parenchymal hematoma: 4% tenecteplase, 16% alteplase (*P*=0.09)	N/A	N/A	Imaging selection used to identify patients most likely to benefit; not designed to prove selection hypothesis

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	End Point Results (Absolute Event Rates, *P* value; OR or RR; & 95% CI)	Relevant 2° end point (if any)	Study Limitations; Adverse Events	Summary Conclusions Comments
EXTEND-IA TNK Campbell BCV, et al. [178] 2018 29694815	**Aim:** to compare IV tenecteplase with the standard IV alteplase in patients with AIS presenting within 4.5 hours of symptom onset with a large intracranial artery occlusion who were also candidates for mechanical thrombectomy **Study Type:** randomized controlled trial **Size:** N=202	**Inclusion criteria:** Onset within 4.5 hours Groin puncture within 6 hours CTA-proven LVO (ICA, M1 or M2, basilar) **Exclusion criteria:** Pre-stroke mRS >3 ICH on initial CT Hypodensity >1/3 of MCA territory on initial CT	**Intervention:** IV tenecteplase 0.25 mg bolus (n=101) **Comparator:** IV 0.9 mg/kg alteplase (10% bolus, remainder over 60 min) (n=101)	**1° end point:** Reperfusion >50% of the involved ischemic territory or an absence of retrievable thrombus at the time of the initial angiographic assessment: 22% with tenecteplase vs 10% with alteplase (adjusted OR 2.6; 95% CI, 2.1-5.9; *P*=0.002 for non-inferiority and 0.03 for superiority). **Safety end points:** ICH: 1% in both groups	•Ordinal shift analysis of 90-day mRS score: Median 2 with tenecteplase and 3 with alteplase (common OR, 1.7; 95% CI, 1.0-2.8; *P*=0.04) •Excellent outcome (mRS score 0-1 at 90 days): 51% with tenecteplase and 43% with alteplase (adjusted OR, 1.1; 95% CI,0.6–2.1; *P*=0.70)	•Differences in functional outcomes were statistically modest •First 80 patients were selected using CTP criteria (core-perfusion mismatch) before the protocol was modified	•Tenecteplase (at a dose of 0.25 mg/kg) was more effective than alteplase in achieving recanalization of a LVO in patients who were candidates for both IV thrombolysis and EVT. •Tenecteplase was also associated with modestly better functional outcomes compared with alteplase.

NOR-TEST Logallo N, et al. [182] 28780236	**Aim:** To establish superiority of tenecteplase 0.4 mg/kg (single bolus) as compared with alteplase 0.9 mg/kg (10% bolus + 90% infusion/60 minutes) for patients with acute ischemic stroke **Study Type:** multicenter, prospective, open-label, blinded end point, phase 3 RCT **Size:** N=1107	**Major Inclusion criteria:** Age 18 years or older; Ischemic stroke with measurable deficit on NIHSS); treatment within 4½ hours of stroke onset, or Wake-Up Stroke-Treatment within 4½ hours after awakening based on FLAIR-DWI mismatch on MRI; eligible for bridging therapy before thrombectomy **Major Exclusion criteria:** Premorbid mRS ≥3; Seizure at stroke onset and no visible occlusion on baseline CT; large areas of hypodense ischaemic changes on baseline CT;	**Intervention:** IV tenecteplase 0.4 mg/kg (single intravenous bolus) n=549 **Comparator:** IV alteplase 0.9 mg/kg (10% bolus + 90% infusion/60 minutes) n=551	**1° end point:** mRS 0-1 at 3 months: tenecteplase : 354/549 (64%) alteplase: 345/551 (63%) OR 1.08; 95% CI, 0.84 - 1.38; *P*=.52 **Safety end point:** Symptomatic ICH at 24-36 hrs: tenecteplase: 3% alteoplase: 2% OR, 1.16; 95% CI, 0.51 - 2.68; *P*=0.70	NIHSS score of 0 or improvement of ≥4 at 24 h: tenecteplase: 41.7% alteplase 38.8% OR, 1.12 (95% CI, 0.89-1.43; *P*=0.97)	• Only mild strokes: Median NIHSS 4 (IQR 2-8) •18% stroke mimics • 4% had symptoms on awakening and had positive DWI-FLAIR mismatch • given its superiority design to detect a 9% difference in the primary end point, this trial was not designed to establish noninferiority	•Tenecteplase at a dose of 0·4 mg/kg has a similar Safety and efficacy profile to alteplase in a stroke population predominantly composed of patients with minor neurological impairment and no major intracranial occlusion.

Parsons M, et al. [180] 2012 22435369	**Aim:** Compare the effectiveness of two different doses of tenecteplase vs. alteplase in acute stroke patients within 6 h of symptom onset and selected by CTP **Study type:** RCT (phase IIb) **Size:** N=75	**Inclusion criteria:** Indication for alteplase; within 6 h of symptom onset; ≥20% mismatch by DWI/PWI or CTP; large intracranial artery occlusion on CTA **Exclusion criteria:** Any contraindications for alteplase	**Intervention:** Tenecteplase, 0.1 mg/kg single bolus, up to 10 mg (N=25) or 0.25 mg/kg single bolus, up to 25 mg (n=25) **Comparator:** Alteplase, 0.9 mg/kg infusion, up to 90 mg (n=25)	**Co-primary end points:** • Percentage of perfusion lesion that was reperfusion at 24 h on MRI: 79% with tenecteplase (both doses combined) vs. 55% with alteplase; *P*=0.004 • NIHSS improvement at 24 h: 8±5 with tenecteplase (both doses combined) vs. 3±6 with alteplase **Safety end point:** No sICH cases	mRS 0–1 at 90 d: 72% with tenecteplase 0.25 mg/kg vs. 40% with alteplase	No differences in ICH or other serious adverse events	Both tenecteplase doses appeared superior to standard-dose alteplase for the studied end points
Haley EC, et al. [181] 2010 20185783	**Aim:** Compare the effectiveness of three different doses of tenecteplase vs. alteplase in acute stroke patients within 3 h of symptom onset **Study type:** RCT (phase IIb/III) **Size:** N=112	**Inclusion criteria:** Indication for alteplase; within 3 h of symptom onset **Exclusion criteria:** Any contraindications for alteplase	**Intervention:** Tenecteplase, 0.1 mg/kg (N=31), 0.25 mg/kg (N=31), and 0.4 mg/kg (n=19) **Comparator:** Alteplase 0.9 mg/kg infusion, up to 90 mg (n=31)	**1° end point:** mRS 0–1: 45% with 0.1 mg/kg, 48% with 0.25 mg/kg, 37% with 0.4 mg/kg and 42% with placebo; *P*>0.3 for all comparisons **Safety end point:** Total of 6 symptomatic ICHs: 3 of 19 (15.8%) in the 0.4 mg/kg group, 2 of 31 (6.5%) in the 0.25 mg/kg tenecteplase group, and none (0 of 31) in the 0.1 mg/kg tenecteplase group; by comparison, there was 1 of 31 (3.2%) symptomatic ICH in the IV alteplase group	N/A	Prematurely terminated due to slow recruitment	The 0.4 mg/kg dose was inferior; the other two doses appeared to be similar to standard dose alteplase