Tenecteplase versus Alteplase for Acute Ischemic Stroke

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Objectives

- Identify the current evidence to support alteplase and tenecteplase in acute ischemic stroke
- Contrast the differences in dosing and administration between alteplase and tenecteplase in acute ischemic stroke
- Enumerate potential advantages of tenecteplase in acute ischemic stroke and identify barriers to implementation

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Completed trials

	N	Population	Time	Imaging	Dose	Results	Year
TNK-S2B	112	NIHSS 10 Age 68	≤ 3h	CT	0.1, 0.25, 0.4 mg/kg, alteplase 0.9 mg/kg	• Day 90 mRS≤1: 45.2%, 48.4%, 36.8%, 41.9% • sICH: 0%, 6.5%, 15.8%, 3.2%	2010
TAAIS	75	LVO mostly NIHSS 14 Age 70	≤ 6 h	CTP mismatch	0.1, 0.25 mg/kg, alteplase 0.9 mg/kg	• Reperfusion: 69.3%, 88.8%, 61.4% • Day 90 mRS≤2: 72%, 44% • sICH: 4%, 12%	2012
TEMPO-1	50	LVO NIHSS 2.5 Age 71	≤ 12 h	CT/CTA	0.1, 0.25 mg/kg	• Recanalization rates: 56%, 61% • Day 90 mRS≤2: 80%, 88% • SICH: 0%, 4%	2015
ATTEST	104	LVO mostly NIHSS 12 Age 71	≤ 4.5 h	CT/CTA/CTP	0.25 mg/kg vs alteplase 0.9 mg/kg	• Penumbra salvaged: 68%, 68% • Day 90 mRS≤2: 36%, 39% • sICH: 2%, 4%	2015
NOR-TEST	1100	NIHSS 4 Age 71	≤ 4.5 h	CT	0.4 mg/kg vs alteplase 0.9 mg/kg	• Day 90 mRS≤2: 77%, 78% • sICH: 3%, 2%	2017
EXTEND-IA TNK	202	LVO NIHSS 17 Age 72	≤ 4.5 h	CT/CTA	0.25 mg/kg vs alteplase 0.9 mg/kg	• Reperfusion: 22%, 10% • Day 90 mRS≤2: 63%, 50% • sICH: 1%, 1%	2018
EXTEND-IA TNK part 2	300	LVO NIHSS 17 Age 72	≤ 4.5 h	CT/CTA	0.25 mg/kg vs 0.4 mg/kg	• Reperfusion: 19.3%, 19.3% • Day 90 mRS≤2: 55%, 57% • sICH 1.3%, 4.7%	2020

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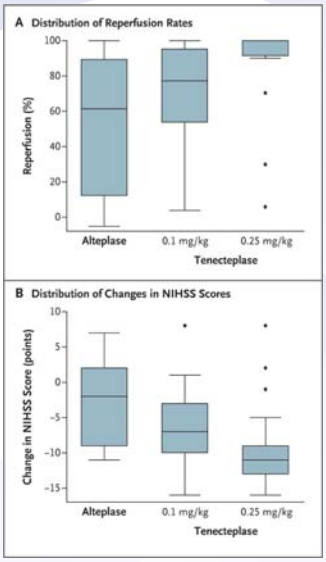
TAAIS



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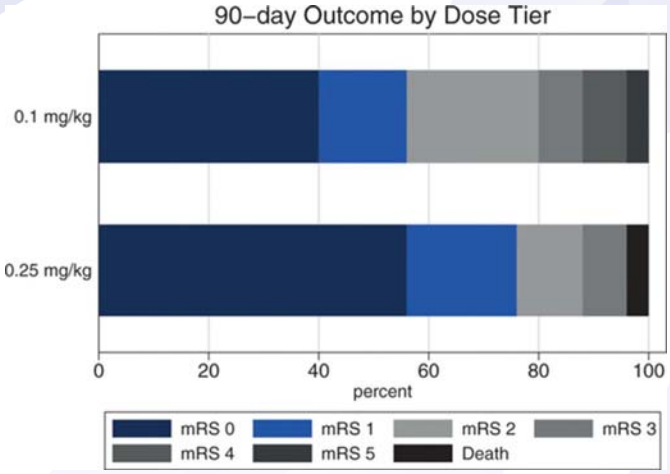
Parsons M et al. N Engl J Med. 2012 Mar 22;366(12):1099-107. PMID: 22435369.

TEMPO-1



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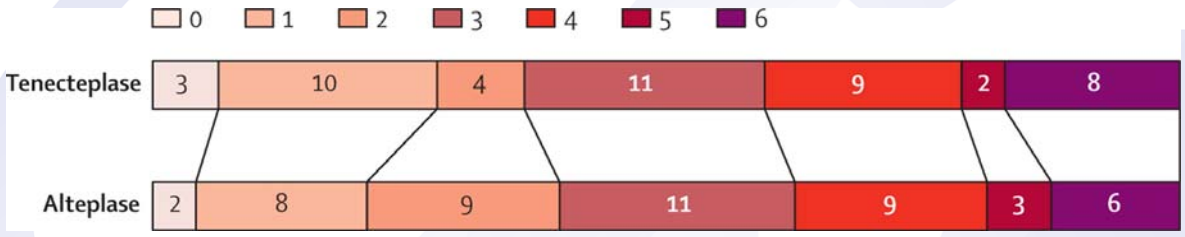
Coutts SB et al. Stroke. 2015 Mar;46(3):769-74. PMID: 25677596.

ATTEST



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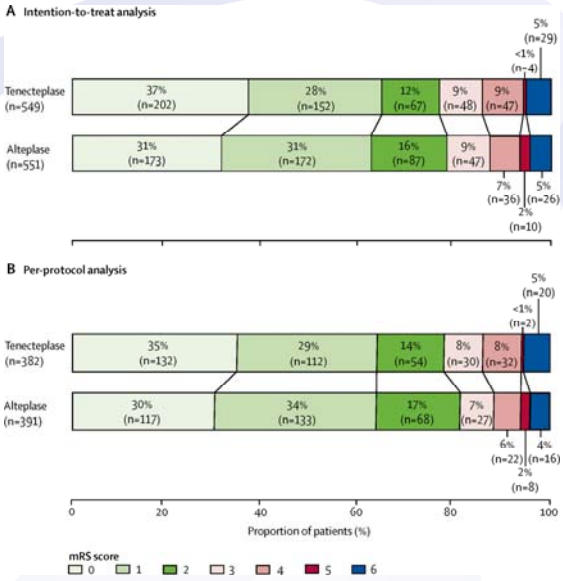
Huang X et al. Lancet Neurol. 2015 Apr;14(4):368-76. PMID: 25726502.

NOR-TEST



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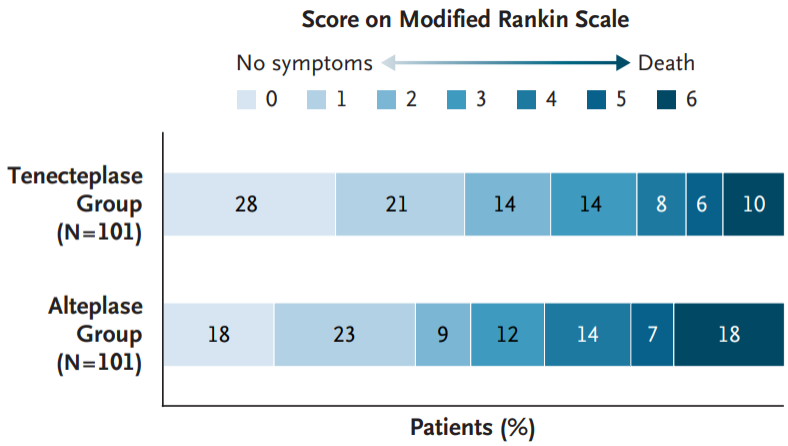
Logallo N et al. Lancet Neurol. 2017 Oct;16(10):781-788. PMID: 28780236.

EXTEND-IA TNK



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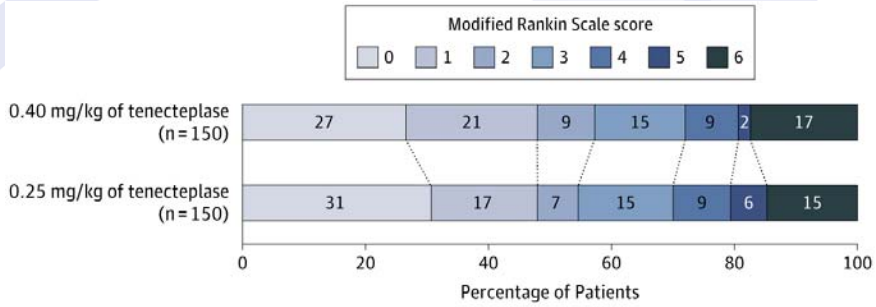
Campbell BCV et al. N Engl J Med. 2018 Apr 26;378(17):1573-1582. PMID: 29694815.

EXTEND-IA TNK part 2



	No. of Patients						
Modified Rankin Scale score	0	1	2	3	4	5	6
0.40 mg/kg	40	32	14	22	13	3	26
0.25 mg/kg	46	26	10	23	14	9	22

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Campbell BCV et al. JAMA. 2020 Apr 7;323(13):1257-1265. PMID: 32078683

Pending trials

	N	Population	Time window	Imaging	Dose	Results	Year
TASTEa	80	Ambulance NIHSS ≥ 1	≤ 4.5h	CT	0.25 mg/kg vs alteplase 0.9 mg/kg	Perfusion lesion on CTP	2021
TWIST	600	NIHSS ≥ 1	≤ 4.5h from wake-up	CT	0.25 mg/kg vs control	mRS at 3 months	2022
TIMELESS	456	LVO NIHSS ≥ 5	4.5-24 hours	Mismatch on CTP or MRI	0.25 mg/kg vs placebo	mRS at 3 months	2022
TEMPO-2	1274	LVO NIHSS ≤ 5	≤ 12h	CT/CTA/CTP/ multi-phase CTA	0.25 mg/kg vs alteplase 0.9 mg/kg	mRS at 3 months	2023
NOR-TEST 2	1342	NIHSS > 5	≤ 4.5h (incl. wake-up)	CT MRI mismatch	0.4 mg/kg vs alteplase 0.9 mg/kg	mRS at 3 months	2023
ATTEST 2	1870	Non-LVO	≤ 4.5h	CT	0.25 mg/kg vs alteplase 0.9 mg/kg	mRS at 3 months	2025

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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.

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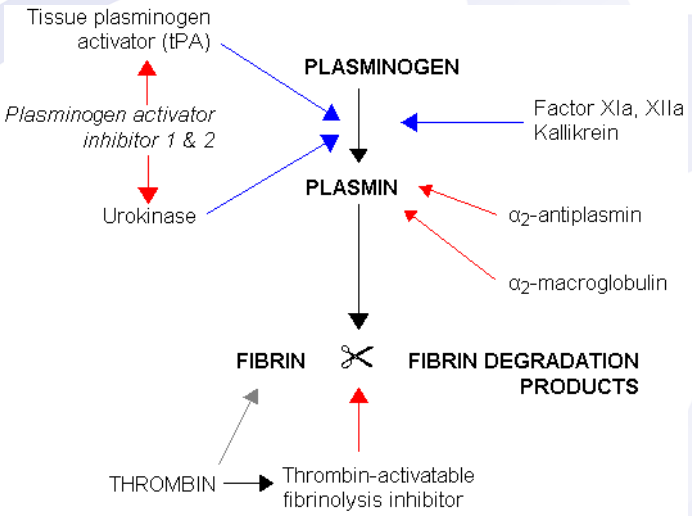
Powers WJ et al. Stroke. 2019 Dec;50(12):e344-e418. Erratum in: Stroke. 2019 Dec;50(12):e440-e441. PMID: 31662037.



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Comparison of alteplase and tenecteplase

	Alteplase	Tenecteplase
Plasminogen activation	Direct	Direct
Fibrin specificity	++	+++
Plasma half life	5 minutes	20 minutes
Dose	0.9 mg/kg with 10% as bolus and 90% as bolus over 60 minutes, maximum 90 mg	0.25 mg/kg (*NORTEST-2 investigating 0.4 mg/kg)* Single bolus over 10 seconds, maximum 25 mg
PAI-1 resistance	Low	80-fold higher than rt-PA
Genetic alteration to native tPA	No (recombinant)	Yes

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Table 1. Thrombolytic Agents

Agent	FDA-Approved Indications	IV Dosing	Comments
Alteplase (rt-PA)	AIS	0.1 mg/kg bolus, then: 0.8 mg/kg infusion over 60 min	ICH: 0.4%-0.9% Max dose = 90 mg (AIS)
	Acute PE	100 mg infusion over 2 h	Fibrin specific
	STEMI	*>67 kg: 100 mg IV (total)* 15 mg bolus over 1-2 min 50 mg over 30 min 35 mg over 60 min *≤67 kg: 100 mg IV (max)* 15 mg bolus over 1-2 min 0.75 mg/kg over 30 min (max 50 mg) 0.5 mg/kg over 60 min (max 35 mg)	Fibrinogen sparing
Reteplase	STEMI	10 units IV push over 2 min Repeat in 30 min	Anaphylaxis ICH: 0.8%
Streptokinase	STEMI	1.5 million units over 60 min	Anaphylaxis ICH not reported
	Acute PE/DVT	250,000 IU IV over 30 min, then: 100,000 IU/h for 24 h (PE) or 72 h (DVT)	
Tenecteplase	STEMI	<60 kg: 30 mg IV bolus 60-69 kg: 35 mg IV bolus 70-79 kg: 40 mg IV bolus 80-89 kg: 45 mg IV bolus >90 kg: 50 mg IV bolus	IV push over 5 sec Most fibrin specific Fibrinogen sparing ICH: 0.9%
Urokinase	Acute PE	4,400 IU/kg over 10 min bolus, then: 4,400 IU/kg/h IV for 12 h	Anaphylaxis ICH: <1%

AIS: acute ischemic stroke; DVT: deep venous thrombosis; ICH: intracerebral hemorrhage; IU: international units; max: maximum; min: minute; PE: pulmonary embolism; rt-PA: recombinant tissue plasminogen activator; sec: second; STEMI: ST-segment elevation myocardial infarction.
Source: References 1, 6-12.

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Duggal RW, Harger NJ. US Pharm. 2011;36(2):HS11-HS16.

Potential advantages of tenecteplase over alteplase

- Better clot lysis due to greater fibrin specificity
- Faster door-in door-out times for satellite hospitals
  - Due to not having to wait for ambulance with personnel who can manage drip
- Faster door to tPA times
  - Due to not having to prepare infusion
- Currently less expensive than alteplase (approximately $6000 versus $7800)
  - Unless using 340B pricing, in which Tenecteplase is $100 less

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Potential disadvantages of tenecteplase

- Need to stock two lytics in ED for different conditions
  - Alteplase only recognized drug for pulmonary embolism
- Dosing errors during conversion period i.e. 0.25 mg/kg versus 0.9 mg/kg
- Tenecteplase not reimbursed if wasted (versus alteplase, which is reimbursed if wasted)

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Steps in getting institutional approval

- Submission to Pharmacy and Therapeutics Committee
- Review with other groups who use lytics in hospital e.g. cardiology, interventional radiology, pulmonary
  - N.B. Tenecteplase does not have a good evidence base for treatment of PE
- Review by Pharmacy and Therapeutics Committee
- Review by Safety Committee
- Review by Legal Department
- At present, total time is likely to be at least 9 months

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Use of tenecteplase for worldwide

- Widely used in Australia
- Regions in Europe
- Africa (Morocco)
- UT Austin
- Cedars Sinai
- Oregon
- Maine Medical Center
- Baystate Medical Center
- MOST trial revising protocol to include tenecteplase in trial
- Others?

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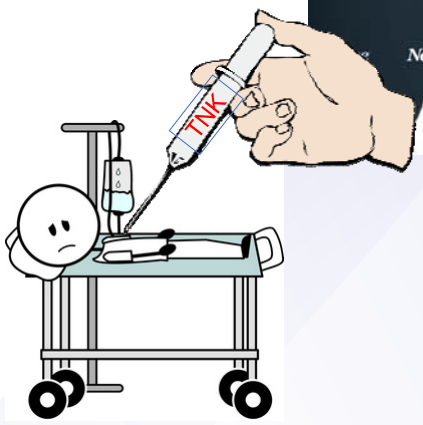

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Conclusions

- Tenecteplase is more fibrin specific than alteplase and appears to be more efficacious in large vessel occlusion
- At this time, data from randomized trials have not definitively proven superiority or non-inferiority of tenecteplase over alteplase in non-LVO stroke
- Tenecteplase can be given as a single bolus in less than 2 minutes, potentially offering time savings in door to treatment time and transfers between hospitals
- The decision to transition to tenecteplase from alteplase should be considered in light of institutional concerns and competing needs

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References

- Haley EC Jr, Thompson JL, Grotta JC, et al. Tenecteplase in Stroke Investigators. Phase IIB/III trial of tenecteplase in acute ischemic stroke: results of a prematurely terminated randomized clinical trial. Stroke. 2010 Apr;41(4):707-11. PMID: 20185783
- Parsons M, Spratt N, Bivard A, et al. A randomized trial of tenecteplase versus alteplase for acute ischemic stroke. N Engl J Med. 2012 Mar 22;366(12):1099-107. PMID: 22435369.
- Coutts SB, Dubuc V, Mandzia J, et al. TEMPO-1 Investigators. Tenecteplase-tissue-type plasminogen activator evaluation for minor ischemic stroke with proven occlusion. Stroke. 2015 Mar;46(3):769-74. PMID: 25677596.
- Huang X, Cheripelli BK, Lloyd SM, et al. Alteplase versus tenecteplase for thrombolysis after ischaemic stroke (ATTEST): a phase 2, randomised, open-label, blinded endpoint study. Lancet Neurol. 2015 Apr;14(4):368-76. PMID: 25726502.
- Campbell BCV, Mitchell PJ, Churilov L, et al. EXTEND-IA TNK Investigators. Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke. N Engl J Med. 2018 Apr 26;378(17):1573-1582. PMID: 29694815.
- Logallo N, Novotny V, Assmus J, et al. Tenecteplase versus alteplase for management of acute ischaemic stroke (NOR-TEST): a phase 3, randomised, open-label, blinded endpoint trial. Lancet Neurol. 2017 Oct;16(10):781-788. PMID: 28780236.
- Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2019 Dec;50(12):e344-e418. Erratum in: Stroke. 2019 Dec;50(12):e440-e441. PMID: 31662037.
- Campbell BCV, Mitchell PJ, Churilov L, et al. EXTEND-IA TNK Part 2 investigators. Effect of Intravenous Tenecteplase Dose on Cerebral Reperfusion Before Thrombectomy in Patients With Large Vessel Occlusion Ischemic Stroke: The EXTEND-IA TNK Part 2 Randomized Clinical Trial. JAMA. 2020 Apr 7;323(13):1257-1265. PMID: 32078683

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