Alteplase for Acute Ischemic Stroke

Introduction

1. Alteplase (rt-PA) has been used for acute ischemic stroke since its approval by the FDA in 1996 after publication of promising results of the NINDS trial
2. NINDS trial has been criticized for its strict inclusion criteria and all major clinical trials since have sought to show benefit in those patients excluded from the NINDS trial
3. Recent re-analysis of the ECASS III trial has been published using independent patient level data

Pharmacology	
Alteplase (Activase)	
MOA	Initiates fibrinolysis by binding to fibrin in a thrombus and converts entrapped plasminogen to plasmin
Dose	• Patient weight <100 kg: 0.09 mg/kg (10% of 0.9 mg/kg dose) as an IV bolus over 1 minute, followed by 0.81 mg/kg (90% of 0.9 mg/kg dose) as a continuous infusion over 60 minutes. • Patient weight ≥100 kg: 9 mg (10% of 90 mg) as an IV bolus over 1 minute, followed by 81 mg (90% of 90 mg) as a continuous infusion over 60 minutes.
Administration	• 10% given as IV bolus over 1 minute; remainder infused over 1 hour
PK/PD	Duration: 1 hour after infusion terminated, bleeding risk can occur past 1 hour Distribution: approximates plasma volume Half-life elimination: 5 minutes Excretion: hepatic and plasma clearance
Adverse Effects	• Intracranial hemorrhage • Angioedema • GI/GU hemorrhage
Drug Interactions and Warnings	• Tranexamic acid, avoid combination • Internal bleeding, thromboembolic events, cholesterol embolization
Contraindications	• Active internal bleeding • Ischemic stroke within 3 months except when within 4.5 hours • Severe uncontrolled hypertension
Compatibility	May be diluted in equal volume with: • 0.9% sodium chloride • D5W NOT compatible with lactated ringers

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Overview of the Evidence

Trials that showed no benefit

	Design/sample size	Time Window	Patient Population	Intervention & Comparison	Outcomes
NINDS-1 (1995)[2]	PRCT (n=291)	≤ 3 hours	• Mean 67 y • Median NIHSS 14 • TTT 0-90 m 47% • TTT 91-180 m 53%	• 0.9 mg/kg rt-PA (Max 90 mg) • Placebo	• No difference in NIHSS score at 24 hours
ECASS II (1998)[3]	PRCT (n=800)	≤ 6 hours	• Median 68 y • Median NIHSS 11 • TTT 0-3 h 19.8% • TTT 3-6 h 80.2%	• 0.9 mg/kg rt-PA (Max 90 mg) • Placebo	• No difference in functional outcomes at 90 days No significant difference in morbidity, despite 2.5 fold ↑ SICH in rtPA group
IST-3 (2012)[4]	PRCT (n =3035)	≤ 6 hours	• 1407 patients >80 y • 201 patients >90 y • TTT 4.2 h	• 0.9 mg/kg t-PA (Max 90 mg) • Placebo	• No difference in functional outcomes at 180 days • ↑ 7-day mortality in rt-PA group (11% vs. 7%) • ↑ SICH in rt-PA group (7% vs. 1%)

Trials that showed benefit

	Design/sample size	Time Window	Patient Population	Intervention & Comparison	Outcomes
NINDS-2 (1995)[2]	PRCT (n=333)	≤ 3 hours	• Mean 69 y • Median NIHSS 14 • TTT 0-90 m 49% • TTT 91-180 m 51%	• 0.9 mg/kg rt-PA (Max 90 mg) • Placebo	• 33% more patients treated with t-PA had mRS 0-1 at 90 days • 2.9% ↑ fatal ICH in tPA group
ECASS III (2008)[5]	PRCT (n =821)	3-4.5 hours	• Mean 65 y • Median NIHSS 9 • TTT 4 h	• 0.9 mg/kg t-PA (Max 90 mg) • Placebo	• 7% more patients treated with t-PA had mRS 0-1 at 90 days • 2.2% ↑ SICH in rt-PA group
WAKE-UP (2018)[6]	PRCT (n =503)	≥ 4.5 hours since LKN	• Mean 65 y • Median NIHSS 6 • TTT 10 h	• 0.9 mg/kg rt-PA (Max 90 mg) • Placebo	• 11% more patients treated with t-PA had mRS 0-1 at 90 days • 8% increase in SICH

EXTEND (2019)[11]	PRCT (n =225)	4.5-9 hours	• Mean 73 y • Median NIHSS 12 • TTT 7.5 hours	• 0.9 mg/kg rt-PA (Max 90 mg) • Placebo	• Stopped early mRs • 0-1 occurred in 35.4% of the tPa group and 29.5% of the placebo group (adjusted OR 1.44; 95%CI 1.01 – 2.06, p=0.04. o In unadjusted primary outcome not statistically significant (OR 1.2, 95% CI 0.82 – 1.76, p =0.35) • More symptomatic intracranial hemorrhage in the tPa group (6.2% vs 0.9%)

Trials that showed harm

	Design/sample size	Time Window	Patient Population	Intervention & Comparison	Outcomes
ECASS-1 (1995)[7]	PRCT (n=620)	≤ 6 hours	• Median 69 y • Median NIHSS 12 • TTT 4.4 h	• 1.1 mg/kg rt-PA (Max 100 mg) • Placebo	• No difference in functional outcomes at 90 days • **Significant ↑ 30-day mortality in T-PA group (22.4% vs. 15.8%)**
ATLANTISB (1999)[8]	PRCT (n =613)	3-5 hours	• Mean 65 y • Median NIHSS 10 • TTT 4.5 h	• 0.9 mg/kg rt-PA (Max 90 mg) • Placebo	• • Stopped early **Trend towards ↑ mortality in rt-PA group (11% vs. 7%)**
ATLANTIS-A (2000)[9]	PRCT (n =142)	≤ 6 hours	• Mean 67 y • Median NIHSS 10 • TTT 4.5 h	• 0.9 mg/kt t-PA (Max 90 mg) • Placebo	• Stopped early More • 4-point improvement at 30 days with placebo than alteplase (75% vs 60%) • Significant ↑ SICH w/in 10 days of rt-PA treatment (11% vs. 0%) • **Significant ↑ 90-day mortality in rt-PA group(23% vs. 7%)**

Epithet (2008)[10]	PRCT (n =101)	3-6 hours	• Mean 71 y • Median NIHSS 13	• 0.9 mg/kg t-PA (Max 90 mg) • Placebo	• Non-significant difference in their primary outcome, which was a disease oriented imaging outcome • **Non-significant difference in mortality (26% with alteplase vs 12% with placebo in patients with perfusion mismatch**

TTT: Time-to-treatment; ITT: Intention-to-treat; PRCT: Prospective Randomized Controlled Trial;

Revisiting the NINDS Study[12]

Reason: the original authors of NINDS rt-PA stroke study (1995) performed further analysis after patients treated earlier did not seem to benefit compared to those treated later, contrary to an expected difference.

However when the baseline NIHSS scores were shown by time-to-treatment instead of treatment group, baseline differences between the rt-PA and placebo groups became apparent.

	Original Report (1995)		**Re-analysis (2000)**			
	Rt-PA	Placebo	0-90 min		91-180 min	
	14	14	Rt-PA	Placebo	Rt-PA	Placebo
NIHSS, mean (SD); median			15.2 (7.2); 15	15.0 (6.7); 14	13.5 (7.7); 12	15.4 (6.9); 15
NIHSS, groups, percent						
0-5			8.3	6.2	19.0	4.2
6-10			19.1	25.5	24.2	27.5
11-15			24.8	21.4	17.0	21.0
16-20			25.5	25.5	21.6	19.8
>20			22.3	21.4	18.3	27.5

The higher median NIHSS baseline scores in the placebo at 91-180 min group resulted in an overestimation of rt-PA's efficacy in the original NINDS trial that even the original authors had to announce in their conclusions of their 2000 reanalysis.

ECASS III Re-analysis[13]

- Previously reported unadjusted analyses were based on modified NIHSS score. The secondary efficacy outcome was no longer significant using the original NIHSS score.
- In analyses adjusted for baseline imbalances, all efficacy outcomes were no longer significant. • Increases in symptomatic intracranial hemorrhage remained significant in 5/6 analyses.

Conclusions

- Currently, the AHA recommends for eligible patients the benefit of alteplase therapy is time dependent, and treatment should be initiated as quickly as possible.
- Baseline imbalances favoring rt-PA in the NINDS trial and the ECASS III trial could be considered controversial, considering these trials were instrumental for drug approval and time window expansion.
- A re-analysis cannot overturn the original findings of a study, only increase or decrease the confidence in the findings it presented.
- The decision to use rt-PA for an acute ischemic stroke should continue to consider potential benefits with consideration for upfront risk of fatal ICH.

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