Overcoming Hesitancy for Lytic Treatment in Stroke, Reviewing the Evolution of This Therapy Over Time

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Disclosures

Today's presentation will include *off label uses;* such uses of medications will be identified as appropriate.

Objectives

1) Know the contraindications for IV lytic administration.
2) Know the difference (including dosing) between Alteplase and Tenecteplase
3) Know the administration risk of Alteplase and Tenecteplase
4) Understand how the use of telemedicine can help with patient selection and lytic administration risk reduction

In the Beginning (The First Trials)

1) NINDS (Part 1 & Part 2) – (concluded October 1994)
   - Placebo vs Alteplase (0.9 mg / kg) within 3 hours of symptom onset
2) ECASS 1 (concluded March 1994)
   - Placebo vs Alteplase (1.1 mg / kg) within 6 hours of symptom onset)
3) **FDA Approves 0.9 mg / kg alteplase for stroke symptoms < 3 hours**
4) ECASS 2 (concluded January 1998)
   - Placebo vs Alteplase (0.9 mg / kg) with two groups: 0 – 3 hours and 3 – 6 hours from symptom onset
5) ECASS 3 (concluded November 2007)
   - Placebo vs Alteplace (0.9 mg / kg) 3 – 4 hours after symptom onset, later extended to 3 – 4.5 hours after symptom onset
6) WAKE-UP (concluded June 2017)
   - Placebo vs Alteplase (0.9 mg / kg) >4.5 hours after last known well with MRI DWI-Flair mismatch

Guidelines and Class/Level of Evidence

Class of Evidence (Strength)

1) Class 1 (Strong)
   - Recommended over other options
2) Class IIa (Moderate)
   - Reasonable and probably better than other options
3) Class IIb (Weak)
   - Consider but no strong evidence for or against
4) Class III: No Benefit (Moderate)
   - Not recommended
5) Class III: Harm (Strong)
   - Causes harm, do try this

Level (Quality) of Evidence

1) Level A
   - High Quality, > 1 RCT
2) Level B-R
   - Moderate Quality, at least 1 RCT
3) Level B-NR
   - Moderate Quality, at least 1 well designed non-randomized control trial
4) Level C-LD
   - Limited Data, primarily retrospective data
5) Level C-EO
   - Consensus of expert opinion and clinical experience

4. 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;50(12):e344-e418. doi:10.1161/STR.0000000000000211

Abbreviations

1) Modified Rankin Score (MRS)
2) National Institutes of Health Stroke Scale (NIHSS)
3) Glasgow outcome scale (GOS)
4) Intracranial Hemorrhage (ICH)
5) Subarachnoid Hemorrhage (SAH)
6) Intravenous Alteplase (rtPA), Intravenous Tenecteplase (TNK)
7) Gastrointestinal (GI)
8) HI 1: Hemorrhagic Infarction with small area of petechiae
9) HI 2: Hemorrhagic Infarction with more confluent petechiae in the infarct
10) PH 1: Petechial Hemorrhage not exceeding 30% of infarct with some spacial occupation
11) PH 2: Petechial Hemorrhage exceeding 30% of infarct with significant special occupation

Modified Rankin Score

1) Grading of symptoms
   - 0 = No symptoms
   - 1 = No significant disability despite symptoms: able to carry out all usual duties and activities
   - 2 = Slight disability: unable to carry out all previous activities, but able to look after own affairs without assistance
   - 3 = Moderate disability: requiring some help, but able to walk without assistance
   - 4 = Moderately severe disability: unable to walk without assistance, unable to attend to needs without assistance
   - 5 = Severe disability: bed-ridden, incontinent, and requiring constant nursing care and attention
   - 6 = Dead

9. Zihni E, McGarry BL, Kelleher JD. Table 1, The modified Rankin Scale (mRS). Published April 29, 2022. Accessed October 23, 2023. https://www.ncbi.nlm.nih.gov/books/NBK580624/table/Ch6-t0001/

Contraindications (Class 3 - No Benefit and Class 3 -Harm)

1) 0 - 4.5 hours since onset with nondisabling stroke
   - NIHSS Score 0-5, Disabling is defined as interfering with activities of daily living or preventing return to work
2) Extensive regions of clear hypoattenuation
   - Insufficient evidence to identify a specific threshold, however large areas of ischemia correlate with an overall poor prognosis and limited benefit of alteplase comparative to risk
3) ICH / SAH
   - Visible ICH or SAH are absolute contraindications
4) Ischemic Stroke within 3 months
   - Use of IV alteplase in this timeframe may be harmful
5) Severe Head Trauma Within 3 Months
   - Absolute contraindication if severe head trauma (penetrating or non-penetrating with hemorrhage) within the last 3 months

4. 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;50(12):e344-e418. doi:10.1161/STR.0000000000000211

Contraindications (Class 3 - No Benefit and Class 3- Harm)

6) Acute Head Trauma
   - Alteplase should not be administered in the presence of post-traumatic infarction
7) Intracranial/intraspinal surgery within 3 months
   - IV alteplase in this timeframe is potentially harmful
8) History of intracranial hemorrhage
   - IV alteplase in patients with prior intracranial hemorrhage is potentially harmful
9) GI Malignancy or GI Bleed within 21 days
   - Patients with a structural GI malignancy or recent bleeding event within 21 days should be considered high risk; IV alteplase administration is potentially harmful
10) Coagulopathy/Anti-coagulant use
   - IV alteplase in stroke patients with platelets <100,000, INR >1.7, aPTT >40s or PT>15s are unknown and alteplase should not be administered
   - In the absence of known thrombocytopenia, coagulopathy, use of anti-coagulant medications: laboratory studies are not needed prior

4. 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;50(12):e344-e418. doi:10.1161/STR.0000000000000211

NINDS Breakdown

1) First major United States Alteplase trial
2) IV Alteplase vs Placebo: at 24 hours how did deficits compare (looking for full resolution or improvement of 4 or more points); overall outcome measures were done with a comparison of Barthel index, Modified Rankin Scale, Glasgow outcome scale and NIHSS
3) What today we call contraindications started as exclusion criteria for this study
4) Alteplase was given at a dose of 0.9 mg/kg (maximum 90 mg), given as 10% initial bolus and the remainder over 60 minutes.

15. Tissue Plasminogen Activator for Acute Ischemic Stroke. *New England Journal of Medicine*. 1995;333(24):1581-1588. doi:10.1056/NEJM199512143332401

NINDS Breakdown

5) Between 1991 and 1994 624 patients underwent randomization
6) At 3 months rtPA group had 12% higher probability of minimal or no disability and 11% increase in the number of patients with an NIHSS of 0 or 1. Evaluation at 24 hours was not predictive of 3-month outcome.
7) 90 days after stroke onset 17% of the rtPA patients were deceased compared to 21% of the patients in the placebo group
8) Symptomatic cerebral hemorrhage in the first 36 hours after rtPA treatment occurred in 6.4% of patients given rtPA and 0.6% of patients given placebo, however, the patients with symptomatic ICH ahd more severe baseline deficits and median NIHSS score of 20. 9% of the patients with intracranial hemorrhage had CT evidence of cerebral edema on baseline CT compared to 4% of the study population as a whole

15. Tissue Plasminogen Activator for Acute Ischemic Stroke. *New England Journal of Medicine*. 1995;333(24):1581-1588. doi:10.1056/NEJM199512143332401

ECASS 1 Breakdown

1) Patients presented within 6 hours of symptom onset received either rtPA at a dose of 1.1 mg/kg (max 100 mg) or placebo
2) CT scan was done at 24 hours and 7 days to evaluate for hemorrhage
3) MRS and Barthel index were used for disability rating at 90 days; the primary goal of this study was to evaluate the morbidity and disability – not complications
4) 6.4% of the randomized trial group had clinical deterioration due to bleeding complications while 19.3% of patients had ICH without clinical deterioration
5) There was a 50% rate of protocol violations due to CT scan misinterpretation
6) In the randomized trial the mortality rate was 18.9%
7) This trial did not separate complications between groups.

3. European Cooperative Acute Stroke Study (ECASS): (rt-PA—Thrombolysis in acute stroke) study design and progress report - Boysen - 1995 - European Journal of Neurology - Wiley Online Library. Accessed October 16, 2023. https://onlinelibrary.wiley.com/doi/10.1111/j.1468-1331.1995.tb00074.x

ECASS 2 Breakdown

1) Goal to evaluate the safety and efficacy of IV rtPA at a dose of 0.9 mg/kg (maximum 90 mg) given within 6 hours of stroke onset (with 10% given as a bolus over 1 minute followed by the remainder as a drip over 60 minutes)
    - Time stratification was done for 0-3 hours and 3-6 hours
2) MRS review at 90 days demonstrated an 8.3% benefit for rtPA when evaluating patients with a 90-day mRS of 0,1 or 2.
3) In the first 7 days there were 6.1% fatalities in the rtPA group and 4.9% fatalities in the placebo group.
4) The overall hemorrhage rate was higher in the alteplase group than placebo (48.4% vs 40.2%) with a higher probability of PH2 in the rtPA group (8.1% vs 0.8%). This however led to no difference in 90-day morbidity/mortality affect
5) At 104 days, 6.1% of patients in the rtPA group and 4.9% of patients in the placebo group had died

7. Hacke W, Kaste M, Fieschi C, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). *The Lancet*. 1998;352(9136):1245-1251. doi:10.1016/S0140-6736(98)08020-9

ECASS 3 Breakdown

1) Study was designed to specifically look at the potential benefit of rtPA in the 3-4.5-hour window after stroke symptom onset
2) Qualifying patients received either 0.9 mg/kg Alteplase (maximum 90 mg given as 10% over 1 minute as a bolus and the remainder over 60 minutes as a drip) and the other group received placebo
3) 52.4% of patients in the Alteplase group had a favorable outcome while only 45.2% of patients in the Placebo group achieved a favorable outcome at 90 days
4) Incidence of symptomatic intracranial hemorrhage was 2.4% in the rtPA group vs 0.2% in the placebo group (any ICH was 27% in the rtPA group and 17.6% in the placebo group).
5) Mortality was 7.7% in the Alteplase group and 8.4% in the Placebo group

14. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke. *New England Journal of Medicine*. 2008;359(13):1317-1329. doi:10.1056/NEJMoa0804656

A Brief Detour To Wake-Up

1) Between September 24, 2012, and June 30, 2017, this trial was run to determine if lytic therapy could be given safely (with imaging guidance) to patients who's last known well was unclear
2) Patients presenting >4.5 hours from last known well whom were not candidates for thrombectomy, had no contraindications to Alteplase therapy and had low baseline MRS and were presenting with an NIHSS of <25; patients also had to be able to get MRI looking for changes on DWI without any changes on FLAIR (mismatch)
3) 503 patients met selection criteria, 254 patients were assigned to receive alteplase and 249 patients were assigned to receive placebo

5. Thomalla G, Simonsen CZ, Boutitie F, et al. MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset. *New England Journal of Medicine*. 2018;379(7):611-622. doi:10.1056/NEJMoa1804355

Wake-Up Trial Outcome

1) The trial was stopped early owing to cessation of funding
2) A favorable outcome was still seen at 90 days in 53.3% of patients in the alteplase group (median 90-day MRS 1); only 41.8% of the placebo group achieved similar outcomes (median 90-day MRS 2)
3) 503 patients met selection criteria, 254 patients were assigned to receive alteplase and 249 patients were assigned to receive placebo
4) 4.1% of patients in the rtPA group expired and 1.2% of patients in the placebo group expired; Symptomatic intracranial hemorrhage rate was 2.0% in the rtPA group and 0.4% in the placebo group

5. Thomalla G, Simonsen CZ, Boutitie F, et al. MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset. *New England Journal of Medicine*. 2018;379(7):611-622. doi:10.1056/NEJMoa1804355

New Kid On The Block (Tenecteplase)

1) Phase IIB/III Trial of Tenecteplase in Acute Ischemic Stroke (2008)
   - Patients <3 hours from symptom onset received either 0.9 mg/kg Alteplase or Tenecteplase dose of 0.1 mg/kg or 0.25 mg/kg or 0.4 mg/kg
2) ATTEST Trial (September 2013)
   - Patients <4.5 hours from symptom onset received either 0.9 mg/kg Alteplase or 0.25 mg/kg Tenecteplase
3) A Randomized Trial of Tenecteplase versus Alteplase for Acute Ischemic Stroke (2011)
   - Patients <6 hours from onset of symptoms received either 0.9 mg/kg Alteplase, 0.1 mg/kg Tenecteplase or 0.25 mg/kg Tenecteplase
   - CT Perfusion and CT Angiogram were used to assist selection (Lesion at least 20% greater than core and LVO)
4) Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke (Oct 2017)
   - Patients <4.5 hours from symptom onset receive either 0.9 mg/kg Alteplase or Tenecteplase 0.25 mg / kg (maximum 25 mg)
5) Tenecteplase versus alteplase for the management of acute ischemic stroke in Norway (NOR-TEST2) – September 2021
   - Patients <4.5 hours from symptom onset (including wake-up candidates with MRI) with NIHSS >/= 6 received either Alteplase 0.9 mg/kg or Tenecteplase 0.4 mg/kg (maximum 40 mg)
6) Tenecteplase versus alteplase in acute ischemic cerebrovascular events (TRACE-2) – July 2022
   - Patients <4.5 hours from symptom onset with NIHSS >/= 5 but </= 25 received either 0.9 mg/kg Alteplase or Tenecteplase 0.25 mg/kg (maximum 25 mg)

Phase IIB/III Trial of Tenecteplase in Acute Ischemic Stroke

1) Trial designed in 2008 to compare standard of care rtPA to TNK at doses of 0.1mg/kg, 0.25mg/kg and 0.4mg/kg in patients presenting within 3 hours of stroke symptom onset. This was designed to try and determine a “best” dose of TNK for future studies by evaluating 3-month outcomes.
2) The trial was prematurely terminated for slow enrollment after 112 patients
    - The 0.4mg/kg dose was seen as inferior after 73 patients due to high levels of symptomatic ICH
    - There was no clear outcome difference between the 0.1 mg/kg dose, the 0.25mg/kg dose and standard of care rtPA, however there was a lower incidence of symptomatic ICH in the 0.1mg/kg group

6. Haley EC, Thompson JLP, Grotta JC, et al. Phase IIB/III Trial of Tenecteplase in Acute Ischemic Stroke. *Stroke*. 2010;41(4):707-711. doi:10.1161/STROKEAHA.109.572040

ATTEST Trial (September 2013)

1) Study looking for radiographic differences between TNK at the 0.25 mg/kg dose and rtPA utilizing CT Angiography and CT Perfusion imaging.
   - Penumbral salvage was similar in both the TNK and rtPA groups without statistical significance
2) Symptomatic ICH rate was 6% in the TNK group and 8% in the rtPA group
   - Total ICH rate was 15% in the TNK group vs 29% in the rtPA group, but sample size was too small for this to represent statistical significance
3) Overall study recruitment for this study was low, data presented suggests non-inferiority, however with the need to cautiously interpret due to low sample size (104 patients)

2. 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;14(4):368-376. doi:10.1016/S1474-4422(15)70017-7

A Randomized Trial of Tenecteplase versus Alteplase for Acute Ischemic Stroke

1) Trial between 2008 and 2011 designed to evaluate standard of care dosed rtPA vs TNK at doses of 0.1 mg/kg and 0.25 mg/kg at <6 hours from symptom onset.
   - This study did also utilize CT Perfusion and CT Angiography to assist in selection
   - Overall sample size was small with 25 patients included in each of the 3 groups
   - Median NIHSS was 14.4 and average time to treatment was around 2.9 hours
   - Patients all had LVO with at least 20% penumbra but with an infarct core <1/3 of the Middle Cerebral Artery territory
   - Patients also had MRI performed at 24 hours and at 90 days to help determine final infarct volume
2) At 90 days 72% of patients in the 0.25 mg/kg TNK group had absence of disability vs 40% of patients in the rtPA group
3) Both TNK groups were superior to rtPA for reperfusion and clinical improvement at 24 hours, lower rate of 24- and 90-day infarct growth on MRI, and lower rate of symptomatic ICH (12% for rtPA vs 4% for TNK).
   - The 0.25 mg/kg group overall had higher benefit rates with a slight increase in ICH rates without a significant impact on mortality compared to the 0.1 mg/kg group

1. Parsons M, Spratt N, Bivard A, et al. A Randomized Trial of Tenecteplase versus Alteplase for Acute Ischemic Stroke. *New England Journal of Medicine*. 2012;366(12):1099-1107. doi:10.1056/NEJMoa1109842

Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke

1) Trial designed to evaluate non-inferiority and/or superiority of 0.25mg/kg TNK vs standard dose of rtPA <4.5 hours from symptom onset with 202 patients enrolled
   - In addition to functional outcome and evaluation of complications this study had a primary outcome looking for >50% restoration of blood flow or complete resolution of retrievable thrombus on imaging done 1-2 hours after treatment with lytics
2) >50% reperfusion or absence of retrievable thrombus occurred in 22% of patients in the TNK group (20/22 patients) and 10% of patients in the rtPA group (6/10 patients)
3) At 90 days median MRS score for TNK was 2 and median MRS score for rtPA was 3
4) Symptomatic ICH rate was low in both groups; 1 patient in the TNK group (who had also received intravenous heparin) and 1 patient in the rtPA group
5) 10 patients in the TNK group expired while 18 patients in the rtPA group expired but neither reached statistical significance
6) Overall conclusion was confirming non-inferiority and a trend towards superiority

10. Campbell BCV, Mitchell PJ, Churilov L, et al. Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke. *New England Journal of Medicine.* 2018;378(17):1573-1582. doi:10.1056/NEJMoa1716405

Tenecteplase versus alteplase for the management of acute ischemic stroke in Norway (NOR-TEST2)

1) Noninferiority trial testing 0.4mg/kg of TNK versus standard rtPA dosing within 4.5 hours of symptom onset
2) Trial was stopped early due to a high proportion of symptomatic ICH between the treatment groups
   - 6% symptomatic ICH in the TNK group vs 1% in the rtPA group
   - 16% mortality at 3 months with the TNK group vs 5% mortality at 3 months with the rtPA group
3) A favorable functional outcome was reported LESS frequently in the TNK group (32% compared to 51% in the rtPA group)

11. 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;16(10):781-788. doi:10.1016/S1474-4422(17)30253-3

Tenecteplase versus alteplase in acute ischemic cerebrovascular events (TRACE-2)

1) Trial tested standard dose rtPA vs 0.25 mg/kg dosed TNK within 4.5 hours of symptom onset; 1430 patients were enrolled in China
2) At 3 months 62% of the TNK patients and 58% of the rtPA patients attained an MRS of 0-1 (primary outcome)
3) Symptomatic intracranial hemorrhage within 36 hours occurred in 2% of the TNK patients and 2% of the rtPA patients
4) 7% of patients in the TNK group expired by 90 days and 5% of patients in the rtPA group expired by 90 days (non-significant)
5) This trial confirms the non-inferiority of the smaller trials but does not support the trend towards superiority seen in smaller trials

12. Tenecteplase versus alteplase in acute ischaemic cerebrovascular events (TRACE-2): a phase 3, multicentre, open-label, randomised controlled, non-inferiority trial - ClinicalKey. Accessed October 16, 2023. https://www.clinicalkey.com/#!/content/journal/1-s2.0-S0140673622026009

Publications Suggesting Resistance

1) In 2018 an electrophysiologist published an opinion article with retrospective literature review making the claim that rtPA did not have the same benefits for ischemic stroke as it does with cardiac patients and has more of a trend towards harm; at the time this caused significant discord between the neurology community and emergency medicine providers
2) The primary reasoning stated for this opinion was the use of MRS or functional outcome as primary endpoint in most stroke studies rather than evaluating straight mortality numbers
3) The secondary reasoning stated in this opinion is the retrospective review of small earlier trials (such as the initial NINDS trial) demonstrating an asymmetry of treatment of mild vs severe strokes and potential skew of outcome as a result
4) Unfortunately, most of the data that was reviewed reflected earlier trials (before 2000) that did not have awareness of how best to select patients more likely to benefit. As demonstrated the large number of recent rtPA vs TNK trials suggest a much lower potential harm from lytic therapy used correctly than is assumed by articles such as this one

13.The Case Against Thrombolytic Therapy in Stroke. Medscape. Accessed October 16, 2023. https://www.medscape.com/viewarticle/895159

Studying Mimics

1) Retrospective cohort study completed evaluation of data from January 1950 up until December 2011 looking at the complications for patients later discovered to have a stroke mimic that were treated with lytic (rtPA) therapy (5518 patients were included, 96 were stroke mimics)
2) Mortality in stroke mimics was lower (2.0% versus 14.4%) but these 2 patients did not appear to die because of lytic therapy (one had epilepsy and died weeks later suddenly at age 86 and the other had a brain tumor at age 75)
3) This study did not utilize MRI consistently which causes some limitation, however the very low complication rate in nearly 100 patients treated with lytic therapy and a final diagnosis that was not consistent with ischemic stroke suggests a very low complication rate in patients treated that do not have ischemic stroke (supported by other smaller retrospective studies and case series that have been presented at conferences in the interval as well)

8. Zinkstok SM, Engelter ST, Gensicke H, et al. Safety of Thrombolysis in Stroke Mimics. *Stroke*. 2013;44(4):1080-1084. doi:10.1161/STROKEAHA.111.000126

What is the Risk?

1) The standard quoted risk of rtPA therapy for ischemic stroke patients is still given as around 5% hemorrhagic complication rate.
2) While most TNK studies seem to demonstrate a lower hemorrhagic complication rate, most of these studies are small and the largest study presented suggests a hemorrhagic complication rate that is about equal but equally lower than in prior rtPA studies
3) Stroke mimic studies are difficult to do without MRI, but this is becoming more common. Available complications rates in patients without ischemic stroke do appear to be incredibly low if not nearly non-existent. This assumes that the provider abides by a clear review of contraindications with the patient before administration and tight control of blood pressure after administration.
4) What the data from the many rtPA vs TNK studies seems to be progressively demonstrating is that the risk of lytic therapy is primarily based on patient selection, with the highest risk being associated with larger completed stroke on CT than initially read by the provider (misinterpretation of imaging). The tighter providers appear to adhere to absolute contraindications, the lower the overall mortality and morbidity appears to be.
    - In this setting it does appear that TNK does demonstrate at least some trend towards a greater morbidity benefit when these restrictions are adhered to

rtPA vs TNK?

1) The standard quoted risk of rtPA therapy for ischemic stroke patients is still given as around 5% hemorrhagic complication rate.
2) While most TNK studies seem to demonstrate a lower hemorrhagic complication rate, most of these studies are small and the largest study presented suggests a hemorrhagic complication rate that is about equal but equally lower than in prior rtPA studies
3) There does appear to be a trend towards morbidity benefit, but larger population data is needed
4) The primary benefit at this point appears to be convenience and cost. TNK is at this point clearly non-inferior and a single bolus of 0.25mg/kg (maximum 25 mg) of medication is much simpler than a 0.9mg/kg administration of rtPA (maximum 90 mg) which requires an initial 10% bolus over 1 minute followed by a 60-minute infusion of the remaining 90% of the drug with need for close monitoring.
5) It is very likely (as we are already seeing) that most facilities will transition completely to TNK due to simplicity and cost in the coming years; I would caution facilities making the transition that there is no significant data for use in pediatric populations and allowance needs to be made for this (and keeping some rtPA on hand) due to this caveat.

What is FDA Approved and What Do We Use?

1) The only lytic administration FDA approved for ischemic stroke is 0.9 mg/kg of Alteplase, maximum dose of 90 mg with 10% administered as a bolus over the first minute when a patient presents with symptoms <3 hours and has no contraindications as listed in the initial NINDS study
2) Alteplase at the same dosing is given between 3 and 4.5 hours with guidelines based on the ECASS trials. FDA approval was never sought technically making this “off label”
3) Tenecteplase has NO FDA APPROVAL in the United States. Based on the multitude of studies currently demonstrating safety and non-inferiority guidelines allow for the use of 0.25 mg/kg not to exceed 25 mg bolus. Many hospitals have changed to this “off label” management due to the simplicity of use and cost reduction compared to Alteplase.
4) Lytic use (either Alteplase or Tenecteplase) for wake-up strokes has NO FDA APPROVAL in the United States. Based on the positive trial data guidelines allow for the use of lytic therapy at >4.5 hours (typically wake-up stroke) when MRI demonstrates a mismatch between DWI and FLAIR sequences. This is still “off label” management

Telemedicine, Beam In the Neurologist

1) Neurologist, particularly Vascular Neurologists are a very limited resource; particularly in rural communities
2) Telemedicine does not replace the onsite physician, but it does allow expertise comparable to having a provider in your facility
3) Stroke management is changing rapidly, ER providers must keep up with multiple fields, maintaining current literature in a field that has now done a complete 180 turn every 2-4 years is quite difficult. Having a Vascular Neurologist able to assist with assessment improves overall safety
4) As noted in the changes throughout the studies from the 1990's through the early 2020's, the overall complication numbers are decreasing. While some of this is due to improved treatments a large majority is the result of a better understanding of selection. This selection is much easier for a Vascular Neurologist who can examine a patient directly and ask a patient and family questions that are needed to optimize therapy and reduce risk. Telemedicine allows this to occur in facilities that do not have a provider on hand.

Telemedicine, Get the Most Out Of It

1) Telemedicine works best with practice and protocols. The use of this is not a replacement for the on-site providers, we can only do so much remotely after all.
2) A protocol should identify patients who have the highest probability for needing treatment. It should then attempt to gather as much of the critical information needed for the Neurologist as possible and then ensure the Neurologist is informed in enough time to not delay evaluation
3) This allows the Neurologist to do an evaluation of the patient with the providers and the information that helps make the best decision. This is what significantly reduces risk of complications (both of treatment and non-treatment) as the correct treatment pathway can be selected cooperatively.
4) Practice Practice Practice, using the equipment and practicing “dummy runs” makes the high stress scenario of an actual acute stroke go more smoothly.

The Future?

1) Studies are ongoing looking for medications that are neuro-protective and possibly neuro-regenerative
2) We will continue to refine choice of patients for both lytic and procedural therapies
3) As seen progressively in the newer trials, imaging is becoming a large component of the selection process and helps to choose the right patients for the right treatments
4) Telemedicine will be playing a larger and larger role in practice. There are fewer specialists, particularly in Neurovascular and use of telemedicine will both allow better access in the ER as well as better patient access for follow-up.

References

1. Parsons M, Spratt N, Bivard A, et al. A Randomized Trial of Tenecteplase versus Alteplase for Acute Ischemic Stroke. *New England Journal of Medicine*. 2012;366(12):1099-1107. doi:10.1056/NEJMoa1109842

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Questions?

Thank You