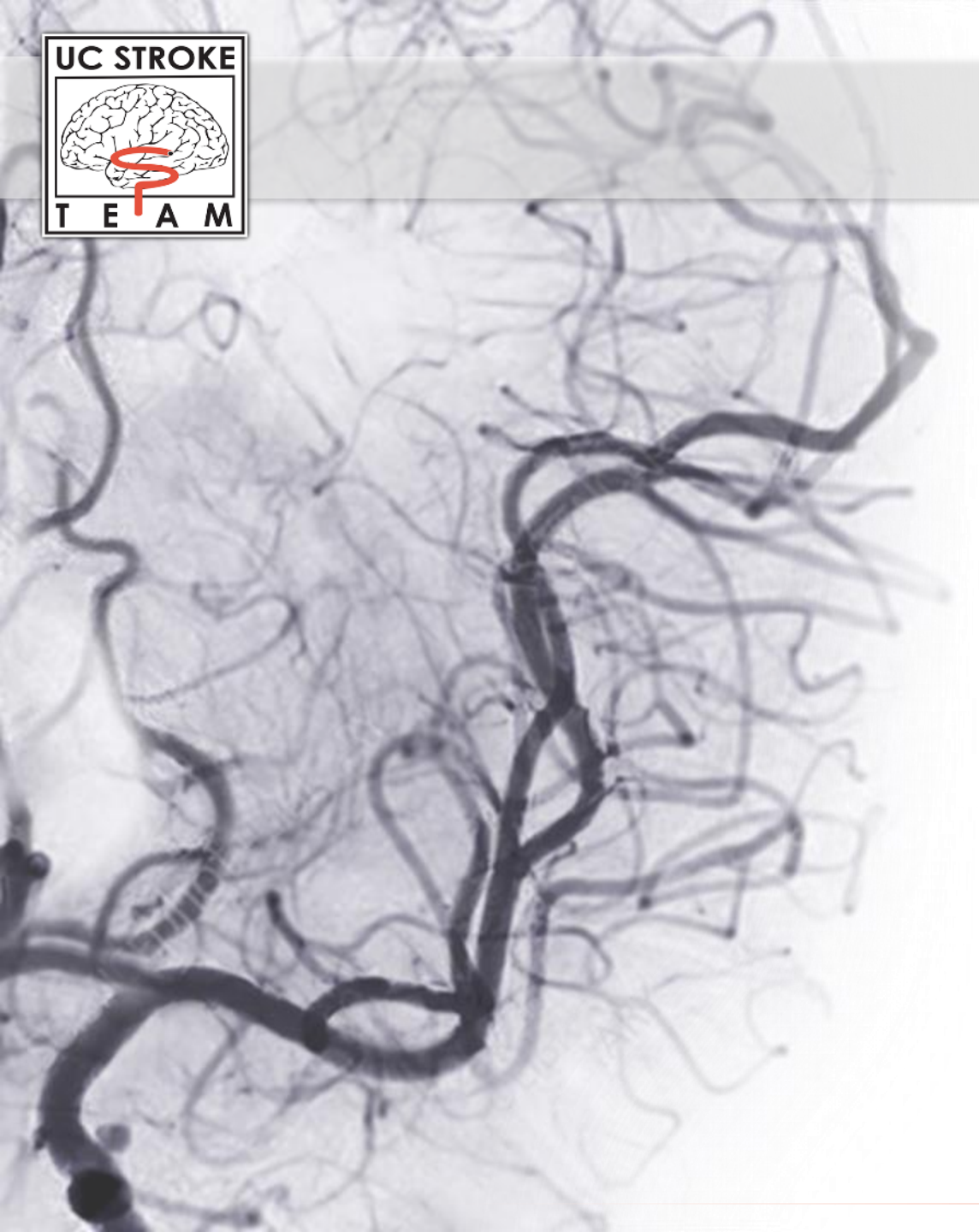

Paradigm Shifts in Thrombolytic Therapy

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Key Note Address

October 25th, 2024

Objectives for Today

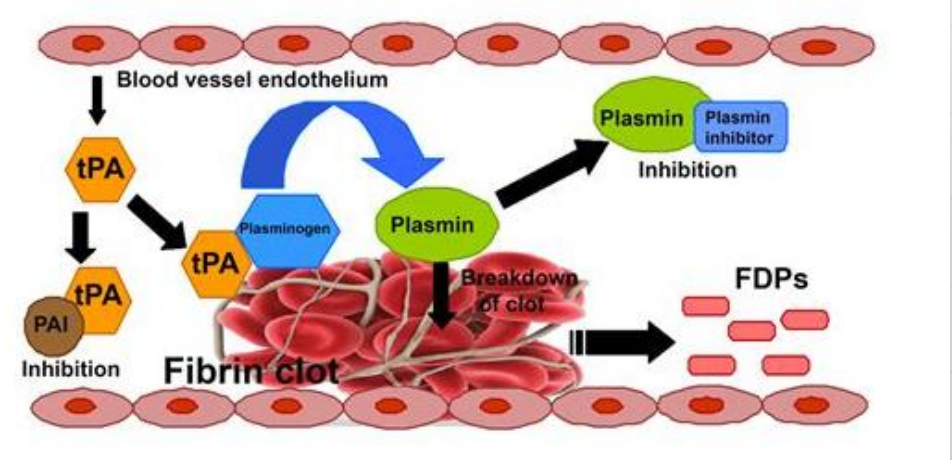
- Understand that patients may qualify for thrombolytic treatment up to 24 hours after last known well
- Understand the utility of CT Perfusion and MRI in treating acute ischemic stroke
- Understand the rationale that led to us treating patients with Tenecteplase vs. Alteplase for acute ischemic stroke

Timeline: Management of Acute Ischemic Stroke

- 1950's - 1970's: Early Investigations of Fibrinolysis
  - Researchers begin exploring plasminogen activators to dissolve blood clots
  - Early studies focus on streptokinase and urokinase as agents to break down clots. These fibrinolytic agents had historically been used in the context of myocardial infarction
    - No specificity for fibrin
    - Contraindicated in stroke due to a higher incidence of intracranial bleeding

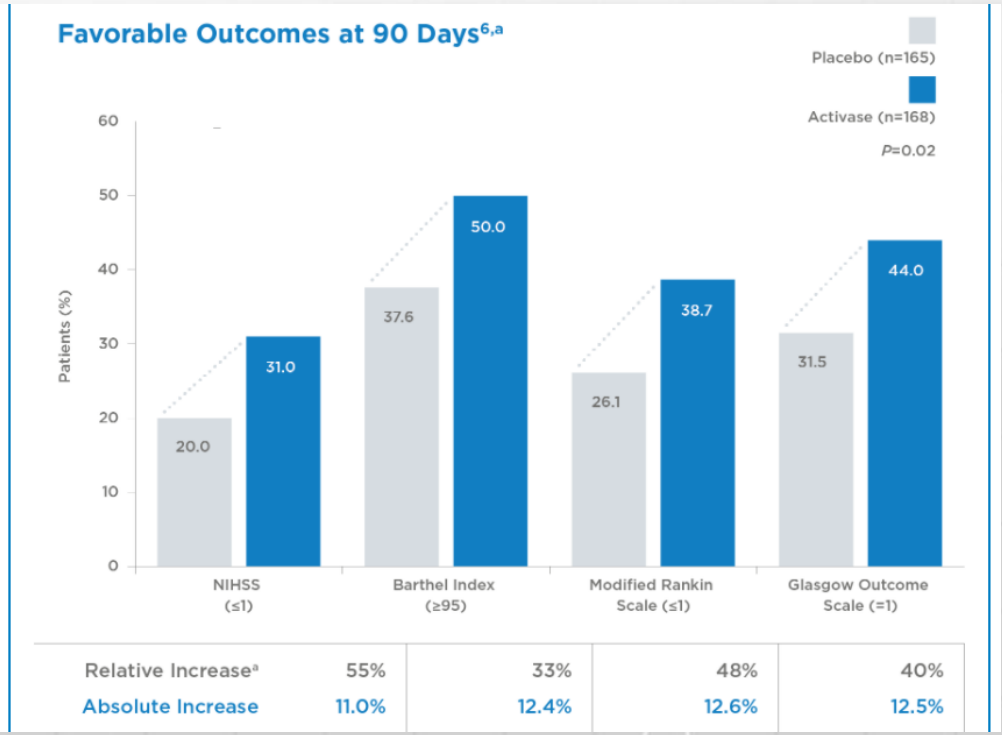
Timeline: Management of Acute Ischemic Stroke

- 1980: Development of Tissue Plasminogen Activator (alteplase; tPA)
  - Researchers at Genentech successfully produce recombinant tissue plasminogen activator (rtPA), a more targeted clot-busting drug
  - tPA catalyzes the conversion of plasminogen to plasmin, which breaks down fibrin clots



Timeline: Management of Acute Ischemic Stroke

- 1990s: Clinical Trials and FDA Approval
  - 1991: The NINDS trial is initiated to investigate the effectiveness of tPA in stroke patients.
  - 1995: the NINDS tPA Stroke Study shows that IV tPA administered within 3 hours of symptom onset significantly improves outcomes in patients with acute ischemic stroke (AIS)
  - 1996: The FDA approves tPA for use in treating AIS – a major milestone in stroke therapy



Marler JR, et al. NEJM 1995

Timeline: Management of Acute Ischemic Stroke

- 2000s: Expanding the Therapeutic Window
  - 2008: The European Cooperative Acute Stroke Study (ECASS III) demonstrated that tPA can be safely administered within 4.5 hours, slightly expanding the treatment window
    - Age 18 – 80 years
    - Median time for administration was ~4 hours
    - NNT for a near complete neurologic recovery = 14
    - 10-fold increase in sICH, no difference in mortality between tPA and placebo groups
  - 2009: the AHA/ASA Guidelines are updated to recommend tPA administration within 4.5 hours of symptom onset for selected patients

Hacke W, et al. NEJM 2008

Timeline: Management of Acute Ischemic Stroke

- 2010's: Integration with Endovascular Therapy (EVT)
  - 2015: Landmark trials like MR CLEAN, ESCAPE, and EXTEND-IA establish that combining tPA with EVT provides significant benefits in patients with large vessel occlusions (LVOs)
  - 2018: the DAWN and DEFUSE 3 trials show that EVT can be effective in patients up to 24 hours after stroke onset, expanding the therapeutic window even further

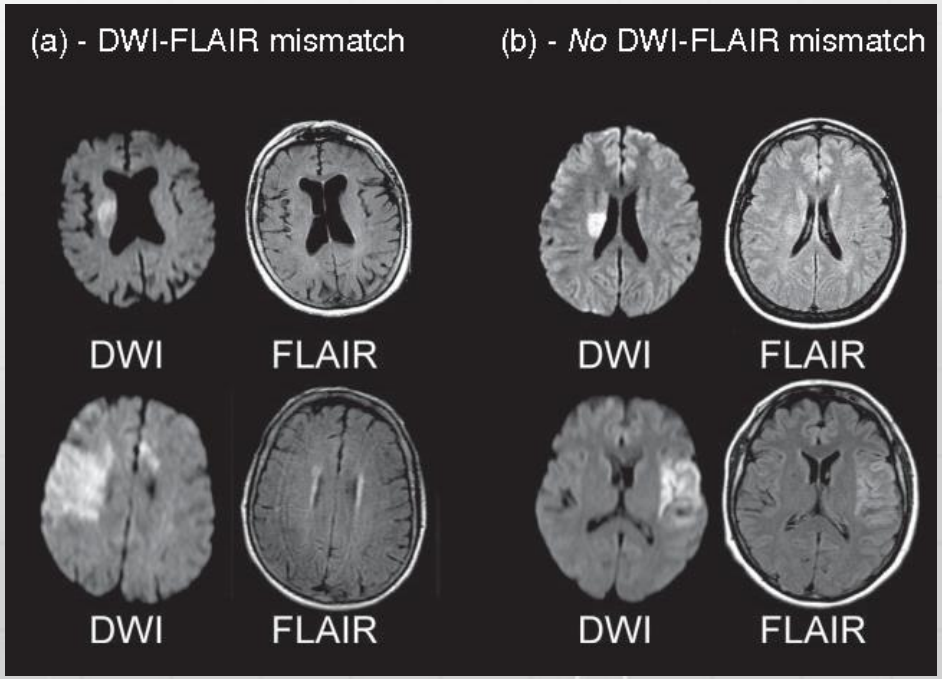
Timeline: Management of Acute Ischemic Stroke

- Usefulness of MRI for patient selection for the use of thrombolytic therapy for AIS
- The WAKE-UP (2018) and MR WITNESS (2019) trials explore the use of MRI to select patients for thrombolytic treatment in acute ischemic stroke, specifically in situations where the exact time of stroke onset is unknown, such as "wake-up strokes" (when a patient wakes up with stroke symptoms and the last known normal time is unclear).
- These trials leverage MRI techniques to identify patients who could still benefit from treatment, even beyond the traditional 4.5-hour time window for intravenous thrombolysis (IVT) with alteplase (tPA).

MRI and patient selection for lytic therapy in AIS

- The Diffusion weighted image (DWI) turns bright when water molecules are restricted (**cytotoxic edema**)

- The Fluid-Attenuated Inversion Recovery (FLAIR) sequence turns bright with **vasogenic edema** (water outside of the cells). This occurs about 6 hours after ischemic event



MRI and patient selection for lytic therapy in AIS

Key Takeaways from Both Trials:

- These trials showed that MRI could allow safe and effective IVT treatment in patients beyond the traditional 4.5-hour window or in patients with unknown stroke onset.
- Improved Outcomes: WAKE-UP demonstrated improved functional outcomes, while MR WITNESS focused on confirming the safety of this approach.
- Impact: These studies suggest that MRI could become a standard tool to guide IVT decisions in stroke patients with uncertain onset times, broadening access to potentially life-saving treatment.

Questions of the 2020's:

- Should we give lytics or skip lytics in patients going for EVT?
  - Direct to EVT trials for stroke focused on bypassing or minimizing the use of IVT with thrombolytics in favor of immediate MT for patients with LVOs.
  - The trials focused on determining if skipping IVT improves outcomes particularly when patients can undergo EVT quickly

Direct to EVT Trials

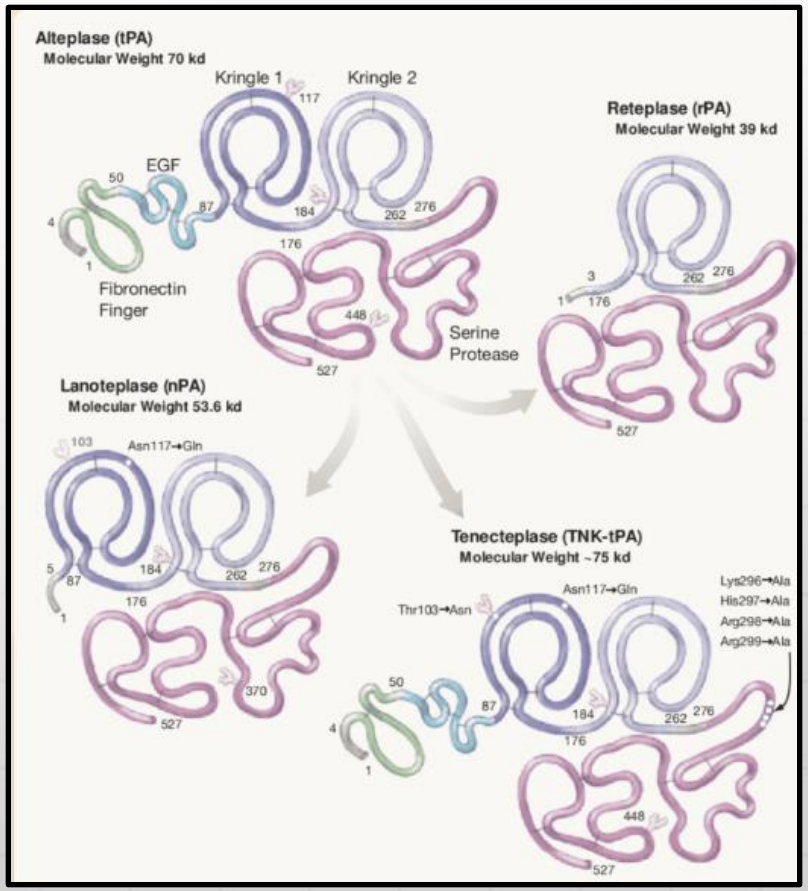
- DIRECT-MT (2020): This Chinese trial compared direct EVT to IVT plus EVT in acute ischemic stroke patients with LVO. Results showed that direct EVT was non-inferior to combined IVT and EVT in functional outcomes after 90 days.
- DEVT (2020): Another Chinese trial similar to DIRECT-MT, comparing direct EVT with IVT followed by EVT. It found direct EVT was non-inferior in achieving good functional outcomes.
- SKIP (2021): This Japanese trial compared direct EVT with IVT followed by EVT. It showed non-inferiority of direct EVT but did not find significant differences in functional independence or safety measures like symptomatic hemorrhage.
- MR CLEAN-NO IV (2021): A Dutch trial that assessed patients randomized to direct EVT versus IVT plus EVT. Direct EVT did not show superiority, and the trial concluded that both approaches yielded similar functional outcomes.
- SWIFT-DIRECT (2021): This trial in Europe tested whether direct EVT could be superior to combined IVT and EVT. It showed non-inferiority but could not establish superiority.

Direct to EVT Trials Take Homes

- Most direct-to-EVT trials have demonstrated that direct EVT is non-inferior to the combination of IVT and EVT, meaning that skipping IVT does not generally lead to worse outcomes.
- No major trial has conclusively shown that direct EVT is superior to IVT plus EVT, but it is considered a viable option, especially in centers where rapid EVT can be performed or when IVT is contraindicated.

Questions of the 2020's: Novel lytics

- How tenecteplase (TNK), a genetically engineered variant of tPA come to take its place?



Characteristic	Alteplase (rt-PA)	Tenecteplase (TNK-tPA)
Immunogenicity	No	No
Plasminogen activation	Direct	Direct
Fibrin specificity	++	+++
Plasma half-life	4-6 min	20 min
Dose	15 mg bolus plus 90 min infusion up to 85 mg	±0.5 mg/kg single bolus over approx. 10 seconds
PAI-1 resistance	Low	80-fold higher than rt-PA
Genetic alteration to native tPA	No (recombinant version)	Yes

Adapted from Ross. *Clin Cardiol* 1999;22:165-171.
* Reteplase resistance described as "Comparable to Alteplase" in Nordt. *Heart* 2003;89:1358-1362.

Questions of the 2020's: Novel Lytics - TNK

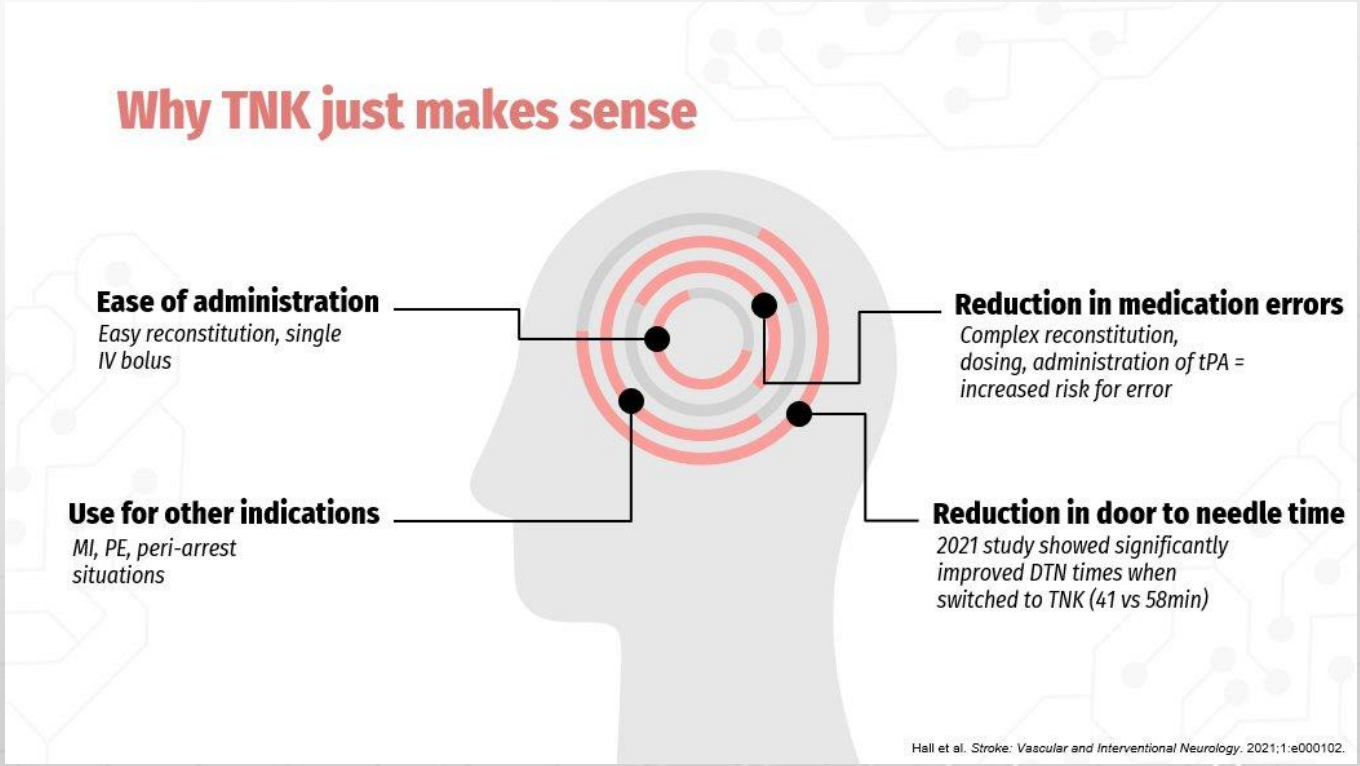
Trial	Patients (n)	Dose of Tenecteplase	Comparison	Primary Outcome	ICH Rates
NOR-TEST (2017)	1,107	0.4 mg/kg	TNK vs. tPA	Non-inferiority, no significant difference in functional outcomes	Similar rates between groups
ATTEST (2016)	104	0.25 mg/kg	TNK vs. tPA	Non-inferiority, trends toward better early recovery with TNK	No significant difference in ICH rates
EXTEND-IA TNK (2019)	202	0.25 mg/kg	TNK vs. tPA (pre-thrombectomy)	Superiority in reperfusion before thrombectomy and better functional outcomes with TNK	Similar rates between groups
TENNECTO (2021)	Open-label	0.25 mg/kg	TNK vs. tPA	Non-inferiority, similar efficacy and safety to tPA	Similar rates between groups
ACT (2022)	1,600	0.25 mg/kg	TNK vs. tPA	Non-inferiority in functional independence (mRS 0-1 at 90 days)	Similar rates between groups

Questions of the 2020's: Novel Lytics: TNK

- When to pull the trigger without FDA approval or clear superiority?
- Our local Stroke Team waited for the results of the ACT Trial (2022)
  - Pragmatic design; Canada
  - Compared TNK vs TPA in AIS patients eligible for thrombolysis within 4.5 hours
  - N = 1600 patients
  - TNK 0.25 mg/kg bolus vs 0.9 mg/kg alteplase
  - Results: TNK was found to be non-inferior to alteplase with regard to functional independence, and there was no significant difference in safety outcomes, including symptomatic ICH or mortality
  - Conclusion: TNK was confirmed to be as safe and effective as tPA, further supporting its potential as an alternative to alteplase in routine stroke care.

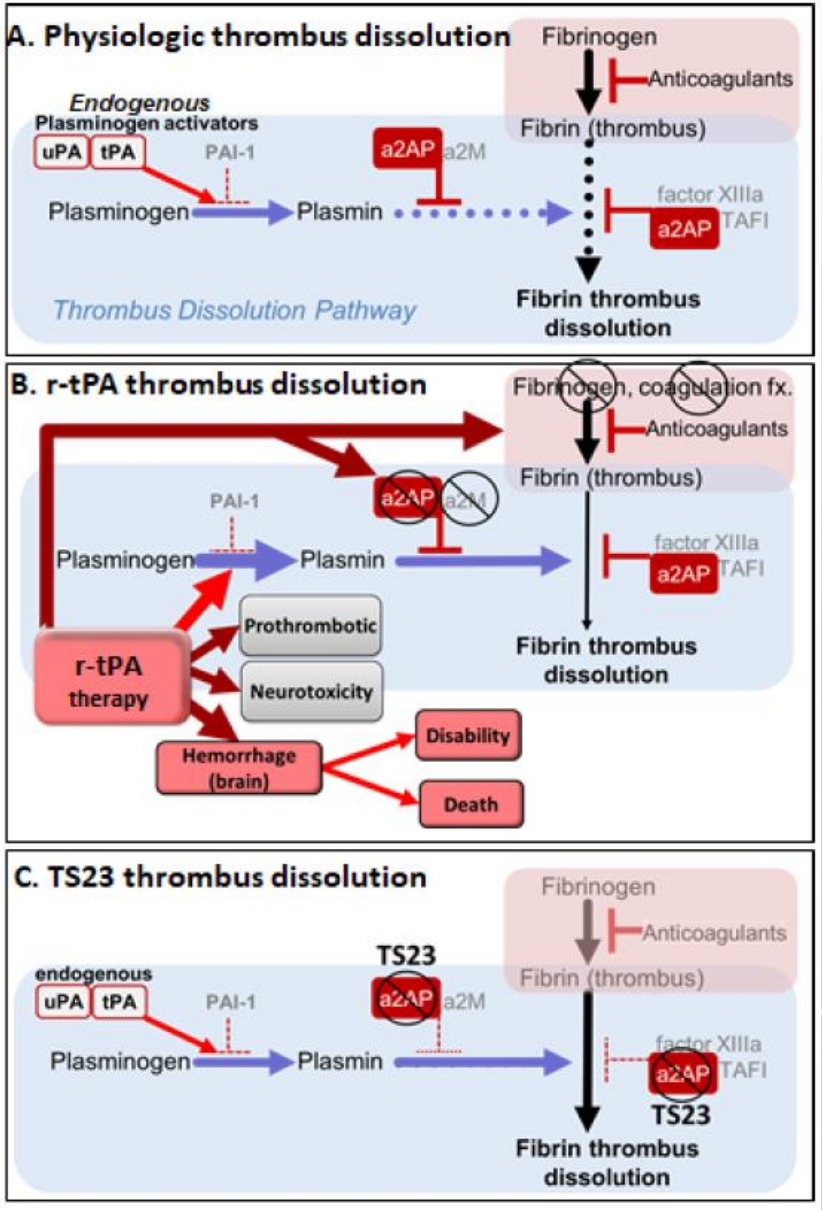
Questions of the 2020's: Novel Lytics

- sICH - Local data
  - 2022 3.3%
  - 2023 3.0%



Novel Lytics: Current Areas of Investigation

- Novel lytics
  - SISTER trial



Adjunctive Therapy to tPA

- The MOST Trial (Multicenter Randomized Controlled Trial of Tenecteplase versus Alteplase in Stroke Thrombolysis) compared tenecteplase to alteplase in acute ischemic stroke patients to evaluate whether tenecteplase is non-inferior or superior to alteplase in terms of functional outcomes and safety.
  - Population: Acute ischemic stroke patients eligible for thrombolysis, treated within 4.5 hours of symptom onset.
  - Design: Randomized, multicenter trial.
- Primary Outcome: Functional independence at 90 days (modified Rankin Scale [mRS] score of 0–1).
  - Tenecteplase was non-inferior to alteplase for achieving functional independence, indicating that tenecteplase is as effective as alteplase in improving outcomes after stroke.
- Secondary Outcomes:
  - Reperfusion rates were similar between the two groups.
- Safety: Symptomatic intracerebral hemorrhage (ICH) rates and overall safety profiles were comparable between tenecteplase and alteplase.
- No significant increase in hemorrhage or other serious adverse events with tenecteplase.
- Conclusion: tenecteplase is non-inferior to alteplase for the treatment of acute ischemic stroke, providing similar functional outcomes at 90 days. Its simpler administration (single bolus) makes tenecteplase a potentially preferable alternative to alteplase in routine clinical practice. The trial adds to growing evidence supporting tenecteplase as an effective thrombolytic agent in stroke care.

Mobile Stroke Unit

- We have discussed how far out we can push the window, but what happens when we treat patients even earlier?
- Published data on MSU vs EMS transported patients have shown ***

Telemedicine

- Even prior to the COVID pandemic telemedicine was being used locally and nationally to enable stroke neurologists to be able to see patients at any emergency department
  - Locally, every hospital in our system had switched by March of 2020, although some of our iPad systems were being used to treat COVID patients at that time.
  - Now every ED, and ICU in the city has it's own "room" in which we can virtually see, examine and discuss acute stroke therapy.
- VIZ.AI – a platform utilized for immediate visualization of head CTs and CT angiograms
  - HIPAA compliant chat
  - AI technology

Areas of Current investigation in Acute Ischemic Stroke Therapy

- Expanding indications for EVT
  - Large core trials
  - TESTED
  - STEP
- Neuroprotective therapies
  - Librexxia

Summary

- The acute stroke therapy of today is not what it was 30 years ago, or even 10 years ago
- Advances in patient selection for thrombolytic therapy have led to increased number of patients having an opportunity for treatment
- Advent of Mobile Stroke Units and AI technology have provided opportunities for patients to be treated faster
- One other bullet point

Thank you!

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