CATRAC Education Symposium

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Expanding the Time Window: Stroke Thrombolysis Beyond 4.5 Hours

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Disclosures

- None
- My thanks to Dr. Warach for his inspiration on this topic

Objectives

- Understand the rationale for extending thrombolysis beyond 4.5 hours.
- Review key clinical trials and imaging techniques.
- Identify patient selection criteria.
- Discuss current guidelines and future directions.

Why 4.5 hours? Where did that come from?

Remember Penumbra - this is important!

- Initial thrombolysis window: **3 hours** (NINDS trial, 1995)
  - Earliest major trial supporting stroke thrombolysis
  - Used CT
  - Window was chosen because early treatment saves more brain!
- Extended to **4.5 hours** by ECASS III trial (2008)
  - These patients had better functional outcomes compared to placebo
  - 4.5 hours balances **maximizing benefit** and **minimizing risks**
  - Risk of hemorrhage increased beyond 4.5 hours
  - Penumbra shrinks; irreversible brain damage increases after 4.5 hours
- 4.5-hour limit became standard clinical guideline

Limitations of the traditional window/rationale for extending the window!

- The 4.5 hour window is too restrictive - many pts who wake up with ‘wake up stroke symptoms’ or have unknown time of symptom onset
- Many pts arrive at the hospital too late due to delayed symptom recognition, transport barriers, or pre hospital restraints
- Door to needle delays within hospitals can further limit the number of eligible patients
- Advanced imaging (CTP, MRI DWI FLAIR mismatch) increasingly used to extend treatment windows beyond 4.5 hours in selected patients
- Wake up and late presenting strokes (4.5 - 24 hours) may still benefit from thrombolysis or endovascular therapy if salvageable tissue is present
- *Data on extended windows continues* - ongoing trials TIMELESS, HOPE, WAKE-UP, EXTEND, MR WITNESS, TWIST, TRACE III, ECASS 4

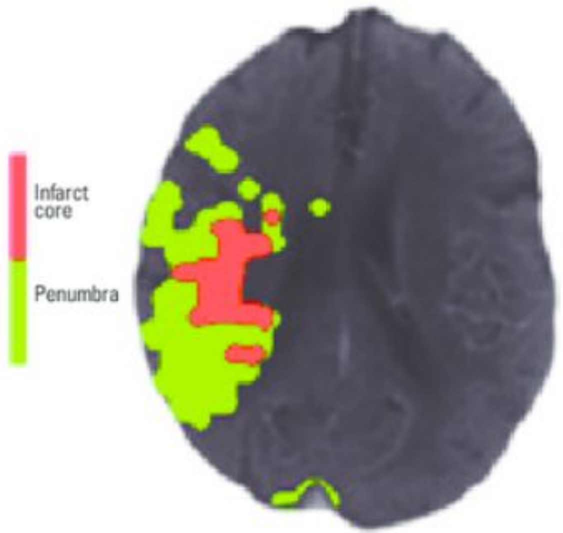
Why Go Beyond 4.5 Hours?

- Stroke is a leading cause of death and disability worldwide.
- Intravenous thrombolysis (IVT) with alteplase/tenecteplase is standard within 4.5 hours.
- But many patients present **after** this window — are they excluded?
- Emerging evidence suggests *careful patient selection* can allow treatment beyond 4.5 hours.

Concept of the Ischemic Penumbra

- Core infarct: irreversible damage.
- Penumbra: hypoperfused but viable tissue.
- Aim of thrombolysis: salvage the penumbra before it progresses to infarction.

Advanced imaging can detect this mismatch.



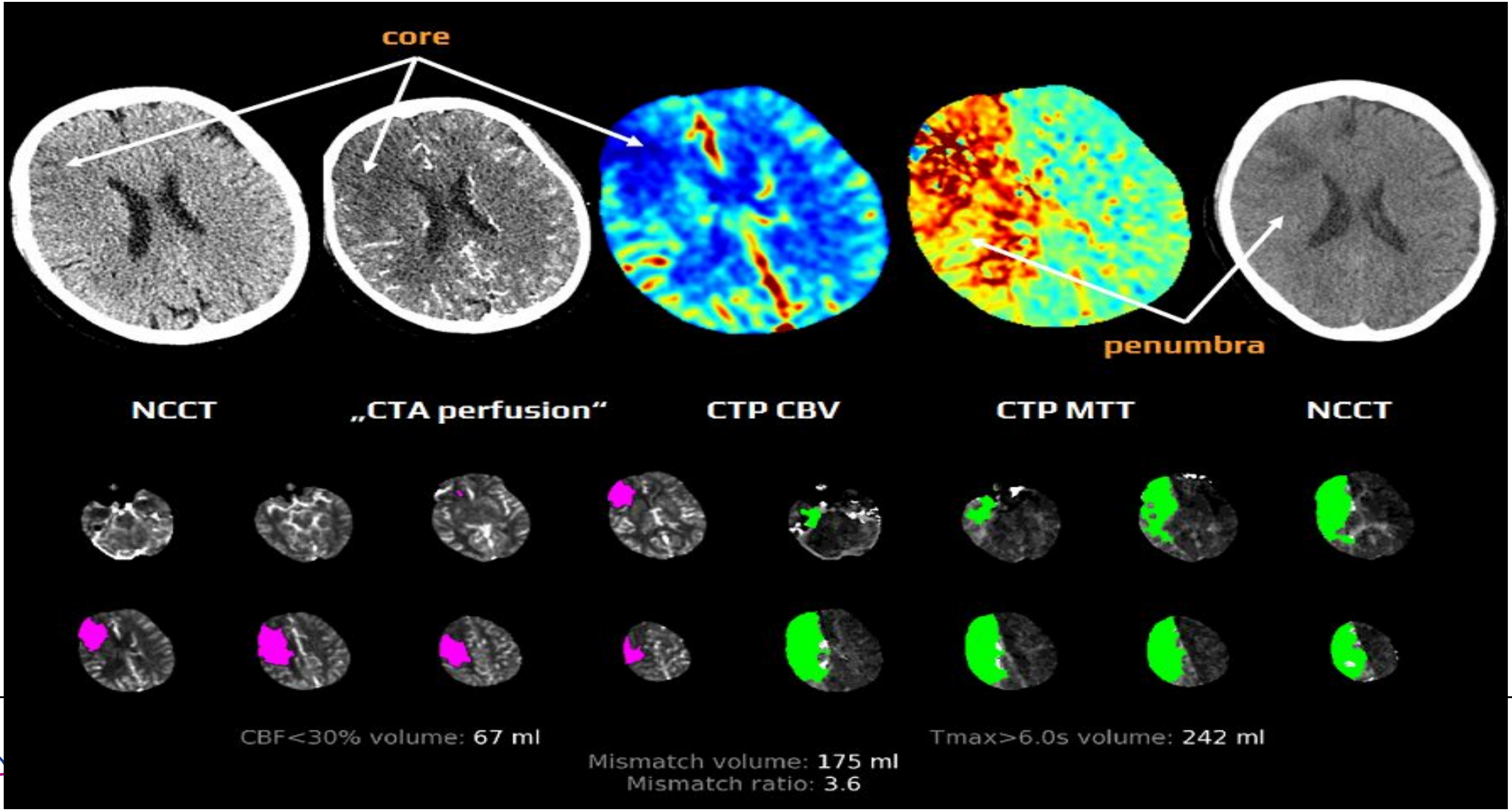
Imaging Techniques and Clinical Criteria for Patient Selection

- **CT Perfusion (CTP)**
  - Measures cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT)
  - Detects core vs penumbra
- **MRI (DWI/FLAIR or PWI/DWI mismatch)**
  - More sensitive but less available and expensive!

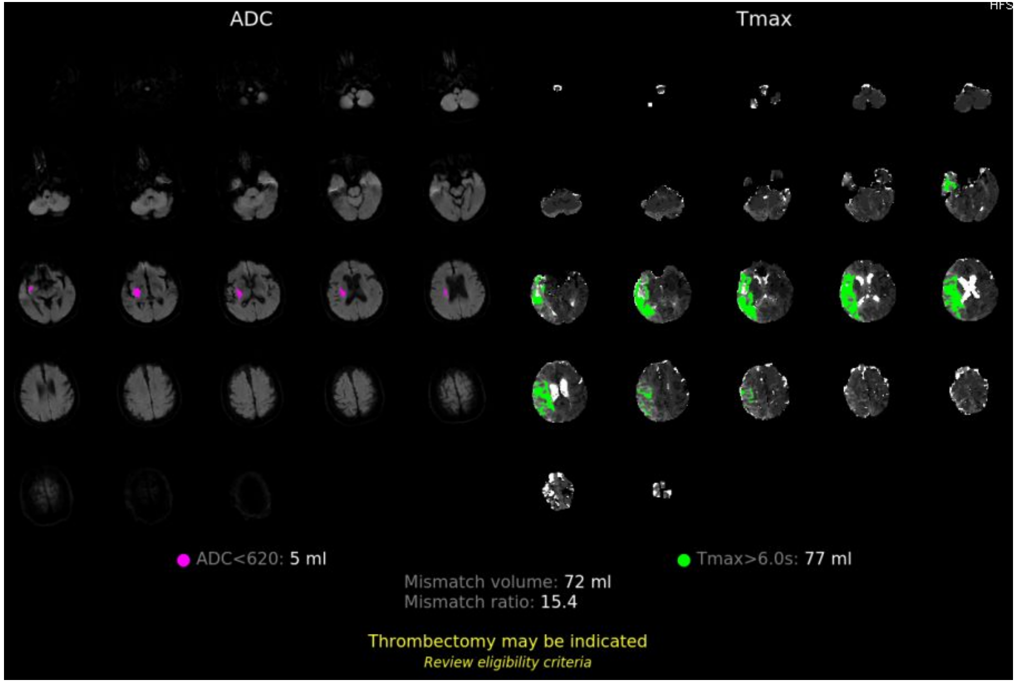
Advanced imaging is key to safe extension beyond 4.5h

- Pre mRS 0 - 2
- Moderate NIHSS preferred (4 - 25)
- No large infarct on imaging (bleeding risk)
- Symptoms consistent with an ischemic stroke (not rapidly improving or minor deficits)
- Exclusion criteria - remains the same
  - Large infarct, uncontrolled hypertension, recent major surgery, GI bleed or high bleeding risk, use of anticoagulants, INR >1.7

Example of advanced imaging - CTP



Example of advanced imaging - MR



- Ischemic core, in pink
- The green shows the at risk brain (the penumbra)
- R middle cerebral artery territory that at risk of infarct
- The "mismatch volume," or the volume that was at risk but not yet infarct, is significant!

DWI - Diffusion weighted imaging - detects acute stroke

FLAIR - Fluid-Attenuated Inversion Recovery - suppresses CSF signal, allows for better visualization of lesions

Stroke on DWI but not on FLAIR = suggests stroke occurred within a therapeutic window

Advanced imaging allows estimation of stroke onset time - this mismatch tells us that the stroke is recent (4 - 6 hours)

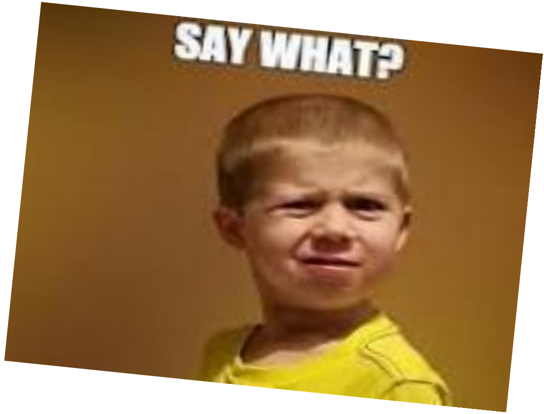
KEY TRIAL - WAKE-UP Trial (2018): Expanding Treatment for Unknown Onset Stroke

- Focused on patients with **unknown stroke onset** (e.g., wake-up strokes)
- Used **MRI DWI-FLAIR mismatch** to estimate stroke age (MRI imaging patterns)
- Alteplase given to MRI-selected patients improved 90-day outcomes
- Demonstrated safe thrombolysis beyond known time window
- Enabled treatment based on **tissue status**, not just time

KEY TRIAL - EXTEND (2019): Extending the Thrombolysis Window to 9 Hours

- Included patients **4.5 to 9 hours** from stroke onset or with wake-up stroke
- Used **CT perfusion** or **MRI perfusion-diffusion mismatch** to identify salvageable brain tissue
- Alteplase treatment improved functional outcomes at 90 days vs. placebo
- Slightly increased risk of symptomatic intracerebral hemorrhage, but benefits outweighed risks in selected patients
- Supported thrombolysis based on **tissue viability** rather than strict time limits

Current Guidelines (AHA/ESO)



AHA/ASA 2023 Guidelines:

- Recommend intravenous alteplase within 3 hours for eligible patients.
- Support treatment in the 3–4.5-hour window for patients under 80 years without contraindications.
- Emphasize rapid treatment initiation; delays may reduce efficacy.

ESO 2021 Guidelines:

- Advocate for intravenous thrombolysis in extended time windows based on advanced imaging.
- Recommend using CT perfusion or MRI to identify salvageable tissue.
- Highlight the importance of advanced imaging in late or unknown onset strokes

Modern trials focused on extended window thrombolysis

WAKE-UP 2018	EXTEND Trial (2019)	DEFUSE 3 Trial (2018)	DAWN Trial (2018)	MR WITNESS Trial (2022)	THAWS Trial (2014–2017)	POSITIVE Trial (2013–2018)	TIMELESS (2024)	HOPE Stroke Trial (2024)
Patients with unknown stroke onset (e.g., wake-up strokes)	Patients within 4.5 to 9 hours of symptom onset or wake-up strokes	Patients with salvageable brain tissue within 6 to 16 hours of symptom onset	Patients with salvageable brain tissue within 6 to 24 hours of symptom onset	Patients with acute ischemic stroke within 24 hours of symptom onset	Patients with acute ischemic stroke within 4.5 to 9 hours of symptom onset or wake-up strokes	Patients with acute ischemic stroke within 12 hours of symptom onset	Patients with acute ischemic stroke due to large vessel occlusion (LVO) in the anterior circulation. Treatment window 6 - 24 hours	Adults with acute ischemic stroke presenting between 4.5 and 24 hours after symptom onset.
Intravenous alteplase guided by MRI DWI-FLAIR mismatch	Intravenous alteplase guided by MRI DWI or CT/MR perfusion imaging	*Endovascular thrombectomy*	*Endovascular thrombectomy*	Intravenous alteplase guided by MRI DWI-FLAIR mismatch	Intravenous tissue plasminogen activator (tPA) guided by MRI DWI or CT cerebral blood flow	Endovascular thrombectomy	Tenecteplase (TNK): Single IV bolus of 0.25 mg/kg (maximum 25 mg). Compared to placebo (saline).	Intravenous alteplase (standard thrombolytic agent) plus standard care,
Significant improvement in functional outcomes at 90 days; low risk of symptomatic intracerebral hemorrhage (sICH)	Positive trend towards improved functional outcomes; trial stopped early due to publication of WAKE-UP results	Significant improvement in functional outcomes; supported the use of advanced imaging to select patients for thrombectomy	Significant improvement in functional outcomes; extended the treatment window for thrombectomy	Positive trend towards improved functional outcomes; further research needed	No significant difference in functional outcomes; highlighted the need for further research in this time window	No significant difference in functional outcomes; underscored the importance of patient selection and timing	Tenecteplase did not improve functional outcomes compared to placebo in this selected population of LVO stroke patients 6–24 hours after onset who were ineligible for thrombectomy.	Demonstrated that intravenous alteplase, administered between 4.5 and 24 hours post-stroke in patients selected by CT perfusion for salvageable tissue—and who were not candidates for thrombectomy—significantly improved functional outcomes (mRS 0–1) at 90 days.

Risks & Limitations of Extended Window

- Increased risk of **symptomatic intracerebral hemorrhage** (sICH)
- Potential for **hemorrhagic transformation** of infarcted tissue
- Requires **advanced imaging** (CT perfusion, MRI), which may not be widely available
- Not all patients have **salvageable penumbra** beyond 4.5 hours
- **Delays** in imaging and treatment can reduce benefits
- Need for **trained personnel** and infrastructure
- Limited data in certain populations (e.g., elderly, severe strokes)

Patient selection is SO important!

Discussion - Unanswered questions

Optimal thrombolytic agent in the extended window -

- Is TNK superior to alteplase beyond 4.5 hours?
  - Alteplase has been studied in EXTEND, ECASS4, and WAKE-UP but TNK data is limited
  - TIMELESS trial (TNK 4.5 - 24 hours) may clarify TNKs role
    - *TNK has been proven as safe and potentially more effective that alteplase (2024)*
- Should TNK be the preferred agent due to its longer half-life and easier administration?
  - TNK is logistically easier and evidence to suggest it has a superior safety profile than alteplase

Best imaging based selection criteria -

- MRI (WAKE-UP) v CTP (EXTEND, ECASS4) v NCCT ASPECTS
  - Are the CT options optimal?

Discussion - Unanswered questions

- What is the true risk of sICH in extended windows?
    - EXTEND reports a higher rate of sICH (6.2%) v standard window (3 - 5%)
        - Should stricter exclusion criteria be used for older pts or those with comorbidities?
    - Is the benefit of late window worth the increased hemorrhage risk?
        - We know that EVT is safe for LVO beyond 4.5 hours- upto 24 hours for some patients
        - Should thrombolysis be avoided in patients with large cores? *YES!*

- Can thrombolysis + EVT improve outcomes beyond 4.5 hours?
    - EXTEND IA TNK showed better reperfusion before EVT with TNK v alteplase in standard timeframes
        - Would late window TNK before EVT improve outcomes or increase bleeding risk?
    - Are some pts better off with EVT alone beyond 4.5 hours?
        - DAWN, DEFUSE 3 showed clear benefit for EVT beyond 6 hours

Discussion - Unanswered questions

- Whats is the maximum time window for thrombolysis?
  - Some wake up strokes (12 - 24 hours) have salvageable tissue
    - Discussion on TIMELESS may redefine the upper limit
  - What about >24 hours?
    - Rare cases with slow infarct evolution COULD exist
    - Experimental and HIGHLY selective!

Future Directions

- Extended Time Windows: Research is exploring thrombolysis up to 24 hours post-symptom onset, with studies indicating potential benefits in select patients without increasing mortality risk
- Wider implementation of perfusion imaging protocols and use of AI to speed up interpretation (e.g., RAPID software): significantly improved the speed and accuracy of identifying salvageable brain tissue
- Mobile stroke units with on-board imaging
- Exploring new thrombolytic agents (e.g., tenecteplase) - which for the most part is standard of care in Central Texas
- Personalized Treatment Protocols: Development of algorithms and decision-support tools to tailor thrombolytic therapy based on individual patient characteristics and imaging results
- Global Implementation Strategies: Efforts to integrate extended-window thrombolysis into stroke care protocols worldwide, ensuring **equitable access** to advanced treatments

Discussion - Future decisions

- Personalized stroke treatment based on imaging rather than rigid time windows may increase eligibility while maintaining safety

- Mobile stroke units, AI driven imaging and streamlined workflows may reduce delays and maximize the benefit of thrombolysis

Conclusion

- Thrombolysis beyond 4.5h is **safe and effective** in **carefully selected patients**
- Imaging is the gateway to expanding the window
- Outcomes improve when treatment is guided by tissue status, not just time
- Need for infrastructure, advanced imaging, training, and protocol adoption
- Stroke Thrombolysis beyond 4.5 hour - The current standard of care
  - IV thrombolytic treatment is of proven benefit and without greater risk than in the earlier time window
  - It should be administered to select patients > 4.5 hrs from TLKW

References

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"Extending thrombolysis to 4.5–9 hours and wake-up stroke using perfusion imaging: a systematic review and meta-analysis of individual patient data." *Lancet*. 2019;394(10193):139–147.
This landmark study demonstrated that intravenous thrombolysis (IVT) is beneficial in patients with acute ischemic stroke (AIS) presenting between 4.5 and 9 hours from symptom onset or with wake-up strokes, provided salvageable brain tissue is identified using advanced imaging techniques.

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"Tenecteplase for the treatment of acute ischemic stroke in the extended time window: a systematic review and meta-analysis." *Therapeutic Advances in Neurological Disorders*. 2024;17:17562864231221324.
This meta-analysis evaluated the efficacy and safety of tenecteplase in the extended time window, suggesting it is a viable alternative to alteplase with a comparable safety profile.

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Alamowitch S, Palaiodimou L, Turc G, et al.

"Tenecteplase in the extended time window." *European Stroke Organisation*. 2023.

This publication discusses the European Stroke Organisation's stance on the use of tenecteplase in extended time windows, highlighting its potential benefits and the need for further research.

Günkan B, Al-Janabi S, Albright K, et al.

"Thrombolysis for ischemic stroke beyond the 4.5-hour window: a meta-analysis of randomized clinical trials." *Stroke*. 2024;55(5):1457–1465.

This systematic review and meta-analysis assessed the outcomes of thrombolysis beyond the standard 4.5-hour window, providing evidence for its efficacy and safety in extended time frames.


SO..
ANY QUESTIONS?
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