AN 'ASE' IN THE HOLE?

AN UPDATE ON THROMBOLYTIC THERAPY IN ACUTE STROKE

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DISCLOSURE
ERICA D. OTTO

- I have no current relationships with commercial entities
- I have a current relationship with the following organizations:
  - Canadian Pharmacists Association: Neurology content peer reviewer (CTC; CPS; CPMA)
  - Heart & Stroke Foundation of Canada: Canadian Stroke Best Recommendations – Acute Stroke Management 7th edition writing group
- I have had past relationships with commercial entities as follows:
  - Member of transplant advisory board (Astellas 2009 – 2011)
  - Received honoraria/grants for project or committee work in transplant (Merk Frosst 2005; Sanofi-Aventis 2006 – 2007; Cangene 2010)
- Speaking Fees for current program
  - I have received a speaker's fee from CSHP-BC for this learning activity

COMMERCIAL SUPPORT DISCLOSURE

- This program has received no financial or in-kind support from any commercial or other organization

LEARNING OBJECTIVES

- By the end of this session, the participant will be able to:
  - Identify the limitations of the historical thrombolytic therapy literature and recommendations
  - Summarize the paradigm shift from *time based* treatment to *tissue based* treatment
  - List the new strategies of thrombolytic therapy currently under investigation in attempts to optimize acute stroke management

GOALS OF THERAPY IN ACUTE STROKE

- Minimize permanent neuron loss
  - Minimize long term disability and restore function
- Avoid complications of therapy

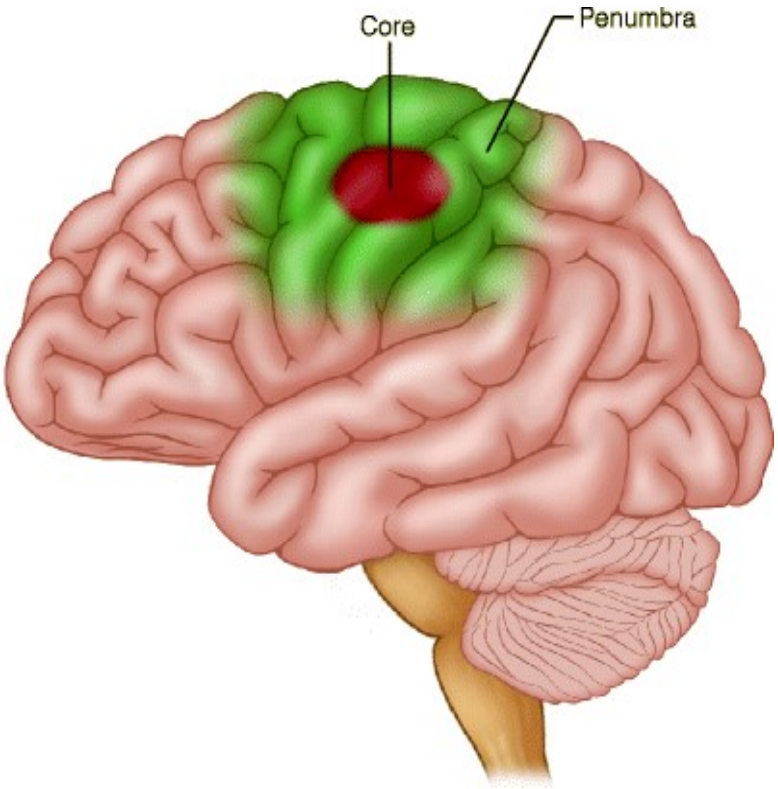
- Approach to <u>acute</u> ischemic stroke
  - Reperfusion
  - BP management
    - Too high BP = ↑ risk of hemorrhagic conversion
    - Too low BP = ↓ cerebral perfusion

- Reduce risk of stroke recurrence
- Prevent complications related to immobility or neurologic dysfunction

- Approach to <u>sub-acute</u> stroke
  - Diagnostics
  - Medical management
    - Atherosclerotic disease
    - Cardioembolic disease

1ST GOAL IN ACUTE STROKE CARE – SOME DEFINITIONS

- Reperfuse the blocked artery
  - Reduce size of infarct core
  - Salvage penumbra
  - Minimize clinical impact of stroke



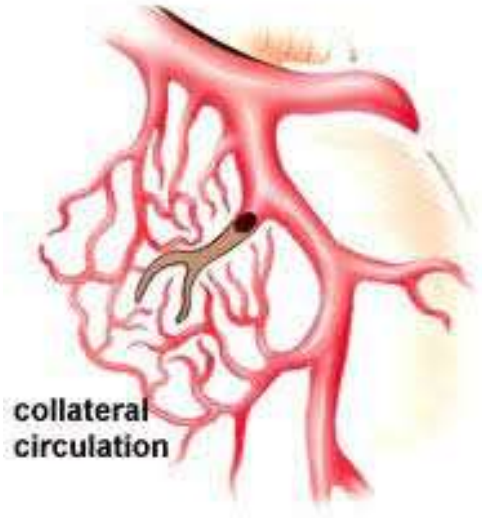
In ischemic regions, there is
an inner zone of infarction
a surrounding zone of ischemia

Core = tissue already irreversibly infarcted or destined to infarct regardless of reperfusion

Stroke 2013;44:2064-89.

THE PENUMBRA

- Hypoperfused tissue surrounding the ischemic core
  - Blood flow is too low to maintain electric activity but sufficient to preserve ion channels
- Collateral vessels can serve as alternate routes of blood supply
- In normal state – no net flow of blood in these communicating arteries
  - Recruited in case of arterial insufficiency
  - Slower flow



Stroke 2011;42:S7-11.

DEFINING CLINICAL IMPACT
NATIONAL INSTITUTES OF HEALTH STROKE SCALE (NIHSS)

- Gold standard for baseline stroke severity rating
- Validated against infarct volume
- Has shown good correlation with stroke outcome and the presence of large vessel occlusions

- 15-item neurologic symptom assessment tool (Scale 0-42; 0= normal function)
  - Mild/minor stroke = 0-7
  - Moderate severity stroke = 8-14
  - Severe stroke = 15-21
  - Very severe = ≥ 22

- Used in clinical trials to adjust outcomes for baseline severity
- Used clinically to monitor baseline severity and early response/deterioration to reperfusion therapy

Stroke 2017;48:513-19.

MODIFIED RANKIN SCALE (mRS) – OUTCOME MEASURE

0 No symptoms as all

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 own bodily needs without assistance

5 Severe disability; bedridden, incontinent and requiring constant nursing care

6 Dead

mRS 0-2 = alive & independant

*photos from google images

THERAPEUTIC ALTERNATIVES FOR REPERFUSION

- Thrombolytic therapy – 1995 onward
  - Alteplase (TPA)
- Endovascular therapy (EVT) - 2015 onward
  - With or without TPA

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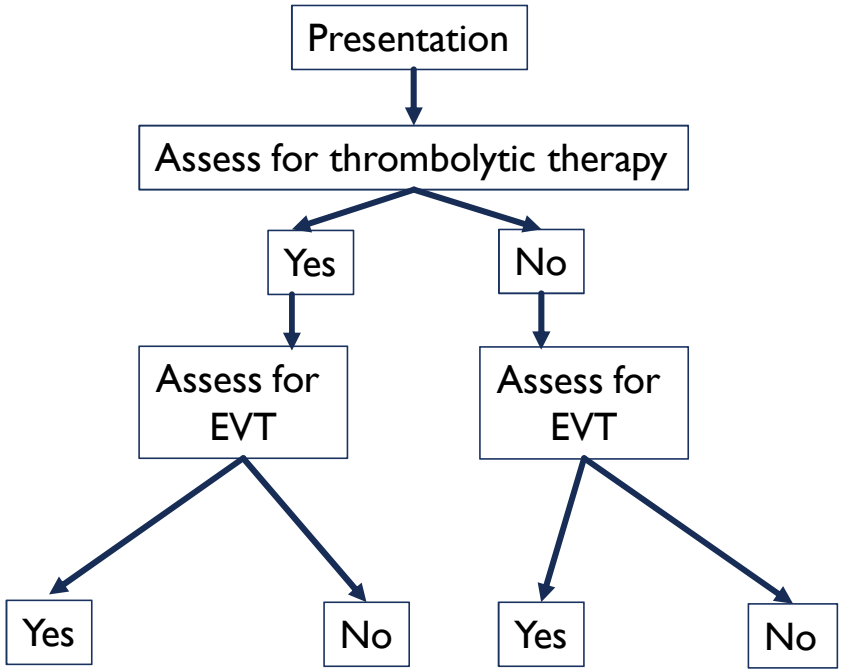
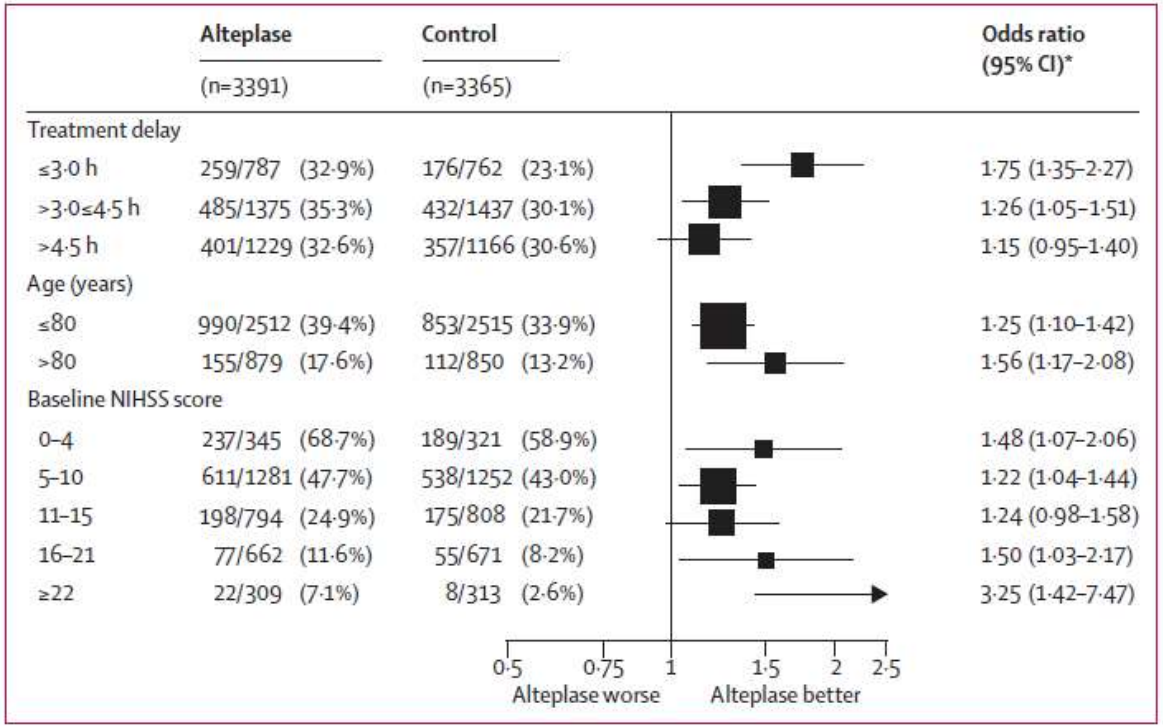
  - With or without TPA



3 LANDMARK TRIALS

Trial	NINDS NEJM 1995;333:1581-7	ECASS-III NEJM 2008;359:1317-29	IST-3 Lancet 2012;379:2352-63
Patients	N=624 Mean 68 yrs; Median NIHSS 14 No anticoag	N=821 <80 yrs, (mean 65); NIHSS median 9-10 No anticoag, No hx stroke+DM	N=3035 >18yrs (53% > 80) *if clear indication for TPA, would be treated and not included
Intervention	TPA 0.9mg/kg (max 90mg) vs. placebo	TPA 0.9mg/kg (max 90mg) vs. placebo	TPA 0.9mg/kg vs open-label control (PROBE design)
Time from symptom onset	< 3h	3 - 4.5h (Median 4h)	< 6h (Mean 4.2h)
Duration of follow up	3 months	3 months	6 months
Favourable outcome	Equiv mRS 0-1 31-50% vs. 20-38% OR 1.7 (95% CI 1.2-2.6; p = 0.008) NNT ~ 8	mRS 0-1 52.4% vs. 45.2% OR 1.34 (95% CI 1.02-1.76; p = 0.04) NNT ~ 14	mRS 0-2 37% vs. 35% OR 1.13 (95% CI 0.95-1.35; p = 0.181)
Symptomatic ICH	6.4% vs. 0.6% (p<0.001) NNH ~ 17	7.9% vs. 3.5% (p=0.006) NNH ~ 22	7% vs. 1% (p<0.0001) NNH ~ 16

EMBERSON ET AL. META-ANALYSIS LANCET 2014;384:1929-35.



	Alteplase (n=3391)	Control (n=3365)	Odds ratio (95% CI)*
Treatment delay			
≤3·0 h	259/787 (32·9%)	176/762 (23·1%)	1·75 (1·35–2·27)
>3·0≤4·5 h	485/1375 (35·3%)	432/1437 (30·1%)	1·26 (1·05–1·51)
>4·5 h	401/1229 (32·6%)	357/1166 (30·6%)	1·15 (0·95–1·40)
Age (years)			
≤80	990/2512 (39·4%)	853/2515 (33·9%)	1·25 (1·10–1·42)
>80	155/879 (17·6%)	112/850 (13·2%)	1·56 (1·17–2·08)
Baseline NIHSS score			
0–4	237/345 (68·7%)	189/321 (58·9%)	1·48 (1·07–2·06)
5–10	611/1281 (47·7%)	538/1252 (43·0%)	1·22 (1·04–1·44)
11–15	198/794 (24·9%)	175/808 (21·7%)	1·24 (0·98–1·58)
16–21	77/662 (11·6%)	55/671 (8·2%)	1·50 (1·03–2·17)
≥22	22/309 (7·1%)	8/313 (2·6%)	3·25 (1·42–7·47)

Figure 2: **Effect of alteplase on good stroke outcome (mRS 0–1), by treatment delay, age, and stroke severity**
*For each of the three baseline characteristics, estimates were derived from a single logistic regression model stratified by trial, which enables separate estimation of the OR for each subgroup after adjustment for the other two baseline characteristics (but not for possible interactions with those characteristics). mRS=modified Rankin Scale.

NNT=8

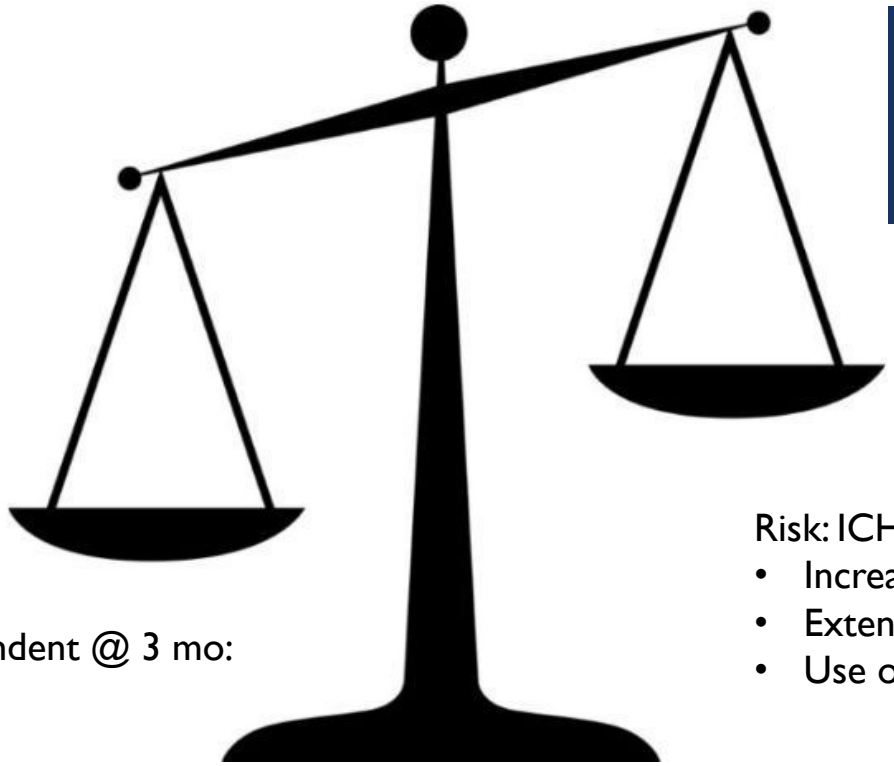
NNT=20

NNH sICH = 18-32 (depending on definition)

CANADIAN STROKE BEST PRACTICE GUIDELINES 2018 (6TH ED)

- **5.3 Intravenous Thrombolysis with Alteplase**
  - i. All eligible patients with disabling ischemic stroke should be offered IV TPA [Evidence Level A]. Eligible patients are those who can receive IV TPA within 4.5 hours of the onset of stroke symptoms [Evidence Level A].
    - Time from last known well (onset of stroke symptoms) less than 4.5 hours before TPA administration.
  - ii. All eligible patients should receive IV TPA as soon as possible after hospital arrival [Evidence Level A]

Int J Stroke 2018;13(9):949-984



Benefit:
Higher chance of alive and independent @ 3 mo:

- Time to treatment

Risk: ICH

- Increased stroke severity
- Extensive early CT changes
- Use of previous antiplatelet therapy

THE UNMET NEED

- Small differences between NNT and NNH
- Narrow time window of effect (< 4.5h)
- TPA contraindications

- Unknown benefit in
  - Mild strokes (NIHSS < 5) – only disabling stroke included in trials
  - Severe strokes (NIHSS > 21) – excluded from trials
  - Large vessel occlusions (LVO) – low recanalization rates identified in EVT literature
  - Very old age – very low numbers in trials

CASE – HP – 90YO RIGHT HANDED FEMALE

- CC: flaccid left paralysis, left facial droop, left neglect and visual field loss, dysarthria

- HPI: Awoke to go to the bathroom at 5am – husband noted nothing unusual at this time; last known fully normal at bedtime (~ 11pm)
  - Awoke in a panic around 8am, motioning to her husband who could not really understand her.
  - Attempted to get out of bed and fell over, husband realized she was paralyzed on the left
  - EMS called

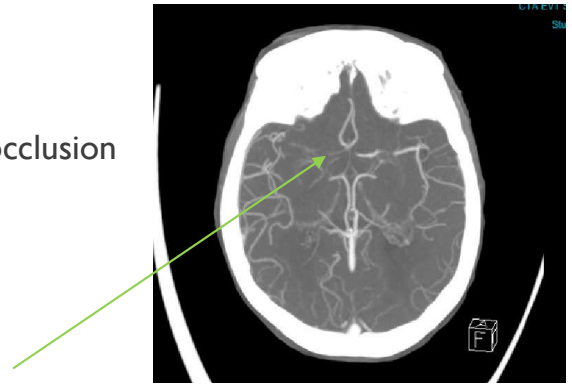
- PMHx:
  - MI with prior stent
  - Afib (confirmed on ECG previously)
  - OA with chronic pain
  - Dyslipidemia

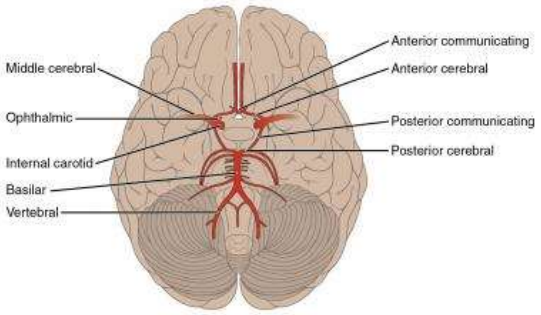
- Meds PTA:
  - Atorvastatin 20mg daily
  - Warfarin 2mg daily
  - Morphine 2.5mg TID prn

CASE CONT'D

- Arrives in NRGH ER at 0850H – straight to CT (Non-contrast CT Head followed by CTA Carotid, Vertebrobasilar, and Intracranial Arteries)
  - Occlusion involving the right ACA terminus/proximal right M1. Good collateral flow.

- Diagnosis:
  - Right MCA ischemic stroke – large vessel occlusion
  - NIHSS = 20





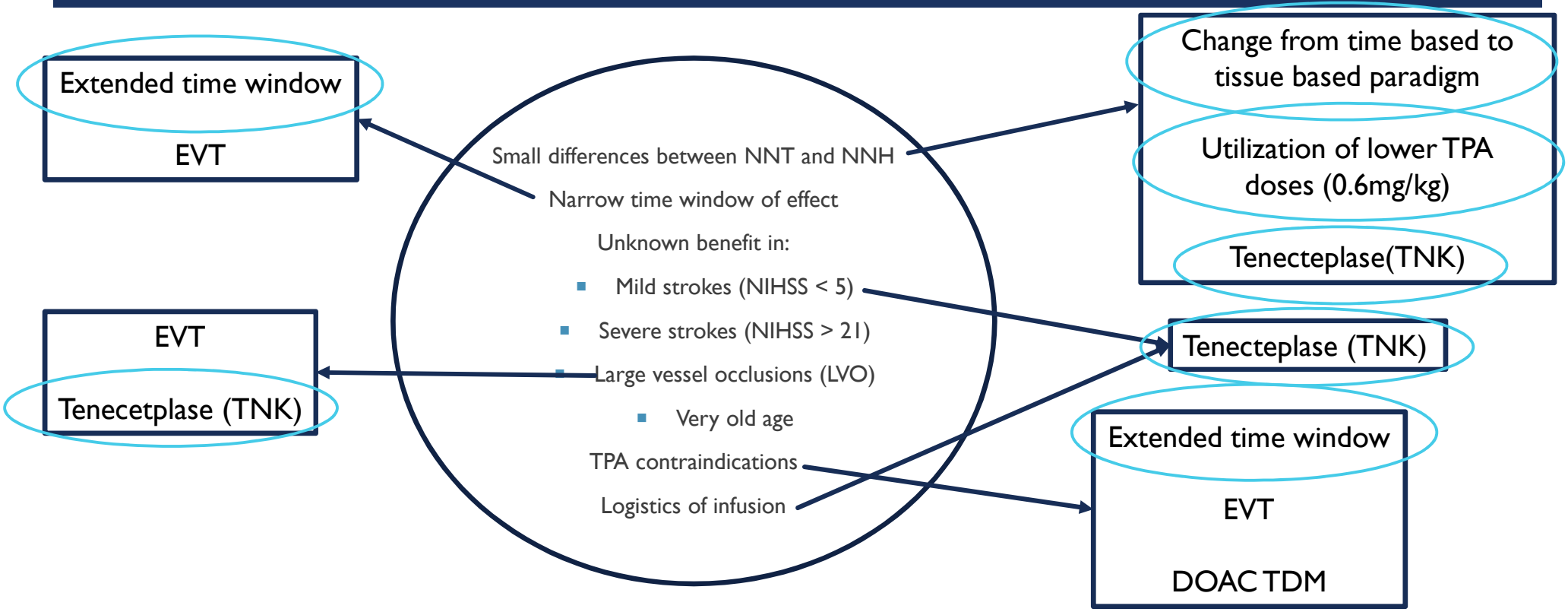
NOW WHAT?

- Therapeutic alternatives:
  - Assess for thrombolytic therapy
  - Assess for EVT

- Considerations:
  - Time of onset – technically a "wake-up"; maybe sometime after 5am (presenting at minimum 3h50min after onset)
  - Warfarin – need INR
  - Age
  - Large proximal occlusion

POLL QUESTION:

ONGOING RESEARCH TO MEET THESE NEEDS:



CHANGE FROM TIME BASED TO TISSUE BASED THERAPY

- Time window = from witnessed time of stroke symptom onset
- Tissue window = biological timing of an evolving ischemia

- Speed of stroke progression differs between individuals
  - Dependant on collateral blood flow, blood pressure, cerebral reserve, size and completeness of infarct core

- Using time alone may lead to missed opportunities for many patients who may benefit from reperfusion
  - All previous thrombolytic literature based on non-contrast CT head

Front Neurol 2018:9, 41. doi.10.3389/fneur.2018.00041
Stroke and Vasc Neurol 2019;4:e000211. doi:10.1136/svn-2018-000211

EVOLUTION OF ENDOVASCULAR THROMBECTOMY (EVT) – ADVANCED IMAGING

- Patient selection
  - Imaging criteria: small infarct core with large penumbra, good collaterals

- New CT and MRI technologies can more accurately estimate tissue viability
  - Non-contrast CT – to rule out hemorrhage
  - CT angiography – to identify large vessel occlusions amenable to EVT
  - CT perfusion or dynamic CTA – to determine perfusion status of brain tissue (total cerebral blood flow (CBF) vs. time to peak blood flow (Tmax)
  - MRI – diffusion-perfusion mismatch (Diffusion weighted imaging(DWI)-fluid-attenuated inversion recovery (FLAIR) mismatch)

Practical Neurology 2019;19:136-42.
Stroke and Vasc Neurol 2019;4:e000211. doi:10.1136/svn-2018-000211

APPLICATION TO CLINICAL PRACTICE

- The paradigm shift from time to tissue based windows of reperfusion may:
  - Identify patients who may benefit from reperfusion outside of traditional time windows
    - Broaden eligibility criteria
    - Could be particularly important in large geographic areas where transport may impact care delivery
  - Identify patients who are unlikely to benefit from reperfusion even within the traditional time windows
    - Reduce risk of hemorrhagic conversion upon reperfusion of infarcted tissue

Stroke and Vasc Neurol 2019;4:e000211. doi:10.1136/svn-2018-000211

EXTENDED TIME WINDOW OF THROMBOLYSIS

- Up to 25% of all ischemic strokes have an unknown time of onset
  - Either upon awakening or due to aphasia
  - Exclusion criteria for thrombolytic therapy

- MRI studies have suggested many wake-up events are probably occurring in the last few hours of sleep

Front Neurol 2014;5:35

WAKE-UP

EFFICACY AND SAFETY OF MRI-BASED THROMBOLYSIS IN WAKE-UP STROKE

Design	**MC, R, DB, PC – 8 European countries**	
Patients	Inclusion: • Clinical signs of acute stroke with unknown onset (on awakening/could not report) • Last known well > 4.5h • 18-80 yo • Independent • MRI DWI/FLARE mismatch (criteria to suggest <4.5h from onset)	Exclusion: • Hemorrhage or lesions larger than 1/3 MCA territory • EVT planned • NIHSS > 25 • Contraindications to TPA
Intervention	TPA 0.9mg/kg (10% bolus then 90% over 1 h; max 90mg)	
Comparator	Placebo	
Outcomes	1° = mRS 0-1 @ 90d 2° = ordinal mRS, "treatment response", symptomatic intracranial hemorrhage (sICH)	

N Engl J Med 2018;379:611-22.

EXTEND

EXTENDING THE TIME FOR THROMBOLYSIS IN EMERGENCY NEUROLOGICAL DEFICITS

Design	**MC, R, PC – Australia/NZ/Finland/Taiwan**	
Patients	Inclusion: • Clinical signs of acute stroke with time of onset 4.5 – 9h or on awakening • >18 yo • Independent • CT perfusion or MRI DWI/FLARE mismatch on RAPID software • Core lesion ≤ 70 mL	Exclusion: • Hemorrhage or lesions larger than 1/3 MCA territory • EVT planned • NIHSS < 4 or > 26 • Contraindications to TPA
Intervention	TPA 0.9mg/kg (10% bolus then 90% over 1 h; max 90mg)	
Comparator	Placebo	
Outcomes	1° = mRS 0-1 @ 90d 2° = ordinal mRS, mRS 0-2 (functional independence), sICH	

N Engl J Med 2019;380:1795-1803.

RESULTS

	WAKE-UP (N Engl J Med 2018;379:611-22)	**EXTEND (N Engl J Med 2019;380:1795-1803)**
Enrollment	Stopped early due to lack of funding Goal N=800	Stopped early when WAKE-UP results released Goal N=310
Patients	N=503 65yo; woke up with symptoms NIHSS 6 ~34% LVO	N=225 72yo; woke up with symptoms NIHSS 11 ~70% LVO
mRS 0-1 @ 90d (TPA vs. placebo)	53.3% vs. 41.8% (p=0.02) OR 1.61 (95% CI 1.09-2.36) NNT = 9	35.4% vs. 29.5% (p=0.04) aRR 1.44 (95% CI 1.01-2.06) NNT = 17
sICH	2.0 vs. 0.4% (p=0.15) NNH = 62	6.2% vs. 0.9% (p=0.05) NNH = 19

SUMMARY OF "EXTENDED TIME WINDOW" LITERATURE TO DATE

- Potential for similar improvement in functional outcome (vs. standard time windows) when thrombolysis offered to:
  - Stroke of unknown onset time if MRI imaging suggests stroke likely to have onset of < 4.5h
  - lower risk of ICH overall in patients selected for thrombolysis on the basis of MRI imaging
  - Note: only 30% of WAKE-UP patients were LVO – these patients should likely go straight to EVT

- Unclear risk vs. benefit of thrombolytic therapy offered to:
  - Stroke of unknown onset time or out to 9 hours from symptom onset with use of CTP/MRI imaging suggesting small core
  - Note: 70% of these patients were LVO – at this point should likely go straight to EVT

BEYOND 4.5 HOURS?

- 2018 guidelines clinical consideration:
  - One recent multi-centre randomized double-blind placebo controlled trial compared TPA to placebo for ischemic stroke patients with unknown time of onset, using MRI selection criteria (DWI/FLAIR mismatch). It included ischemic stroke patients who were not candidates for EVT and who would otherwise have met the criteria for acute IV TPA
  - This trial demonstrates a clinical benefit of IV TPA > 4.5 h from the time the patient was last known well in patients where onset time is unknown (no upper time limit defined).
  - Selection of patients for IV TPA > 4.5 h on the basis of CT, CTA and CTP remains unproven at this time.
  - *MRI scanning can be challenging to obtain urgently and should not delay decisions regarding EVT eligibility.*

Int J Stroke 2018;13(9):949-984

LOW DOSE TPA

- Trying to address small difference between NNT and NNH

- Risk of hemorrhagic transformation/sICH
  - Alteplase: ↑ odds of ICH by factor of 6-7 depending on definition used
  - Mortality = 50%
  - Contributing factors:
    - ↑ stroke severity
    - Extensive early CT changes
    - Use of previous antiplatelet therapy
    - Controversial: ↑ age; ↑ SBP, ↑ blood glucose, Asian race, male sex

Lancet Neurol 2016;15:925-33.
Stroke 2009;40:3067-72.
JAMA Neurol 2014;71:1181-5.
Stroke 2012;43:2293-9.

LOW DOSE TPA

- TPA 0.6mg/kg approved as standard dose in Japan
  - J-ACT study: 0.6mg/kg single arm non-randomized vs. 0.9mg/kg published literature
    - Equivalent clinical outcomes but ↓ ICH rates
  - Higher risk of ICH seen in Asian populations

- Goal
  - to determine if a ↓ dose would show ↓ risk of ICH without compromising efficacy in an international population

NEJM 2016;374:2313-2323. Stroke 2006;37:1810-15.

ENCHANTED

Design	**PROBE, MC, Non-inferiority**	
Patients	Inclusion: • Clinical signs of acute stroke < 4.5h • ≥ 18 yo • Independent	Exclusion: • Standard contraindications to TPA
Intervention	TPA 0.6mg/kg (15% bolus then 85% over 1 h; max 60mg)	
Comparator	TPA 0.9mg/kg (10% bolus then 90% over 1 h; max 90mg)	
Outcomes	1° = death or disability @ 90d (mRS 2-6) 2° = symptomatic intracranial hemorrhage (sICH)	

N Engl J Med 2016;374:2313-23.

ENCHANTED RESULTS

Patients	N=3310 67yo; NIHSS 8 63% Asian; 27% European/Australian; 10% South American
1° = mRS 2-6 @ 90d (0.6mg/kg vs. 0.9mg/kg)	53.2% vs. 51.1% OR 1.09 (95% CI 0.95 to 1.25) (p=0.51) *non-inferiority upper boundary = 1.14
sICH • SITS-MOST definition • NINDS definition	 1.0 vs. 2.1% (p=0.01) 5.9 vs. 8.0% (p=0.02)

N Engl J Med 2016;374:2313-23.

ARE THERE SUBGROUPS WHO MAY BENEFIT?

- ENCHANTED – multiple pre-specified subgroup analyses – consistent results of "not non-inferior" and ↓ ICH
  - No significant difference in treatment effects observed with:
    - Prior antiplatelet use
    - "high risk" patients – older, Asian, severely affected
    - History of prior stroke and DM

- Multiple Post hoc analyses!
  - Only UK participants, on lipid lowering pre-treatment, Korean and bridge to EVT, renal dysfunction, Chinese population only

JAMA Neurol 2017;74:1328-35. J Neurol Sci 2018;387:1-5.
Stroke 2017;48:1877-83.

SUMMARY OF "LOW DOSE" TPA LITERATURE TO DATE

- Has not been shown to be non-inferior to standard dose TPA
  - Numerically similar rates of death and disability at 3 months
- Lower rates of ICH
- Unknown selection criteria of who may benefit from this lower risk of ICH

ALTERNATIVE AGENTS – TENECTEPLASE (TNK)

- Pharmacodynamic advantages
  - Greater fibrin specificity, less disruption of hemostasis
  - Greater resistance to inactivation by plasminogen activator inhibitor-1 (PAI-1)

- Pharmacokinetic advantages
  - Longer free plasma half-life (IV bolus vs bolus and infusion with TPA)

- Practical advantages
  - Time savings (to medical imaging, to EVT suite, to interfacility transfer)
  - Easier to administer (Direct IV bolus over 5 seconds vs. bolus syringe + IV pump set-up for infusion bag, run over 1h)
  - COVID-19? - ↓ staff/patient interaction, no IV pump that accompanies the patient through other hospital departments and wards

Int J Stroke 2018;13:885-92.
JAMA Neurol 2020;77:1203-4.
N Engl J Med 2012;366:1099-107.

NOR-TEST

Design	PROBE, MC, Superiority	
Patients	Inclusion: • Clinical signs of acute stroke < 4.5h (or <4.5h of awakening with symptoms if MRI DWI/FLAIR mismatch) • >18 yo • Independent	Exclusion: • Hemorrhage or lesions larger than 1/3 MCA territory • NIHSS > 25 • Contraindications to thrombolysis
Intervention	TNK 0.4mg/kg IV bolus (max 40mg)	
Comparator	TPA 0.9mg/kg (10% bolus then 90% over 1 h; max 90mg)	
Outcomes	1° = mRS 0-1 @ 90d 2° = ordinal mRS, "treatment response", symptomatic intracranial hemorrhage (sICH)	

Lancet Neurol 2017;16:781-8.

EXTEND-IA TNK

Design	**PROBE, MC, sequential non-inferiority then superiority**	
Patients	Inclusion: • Clinical signs of acute stroke < 4.5h • >18 yo • Independent • Large vessel occlusion and eligible for EVT	Exclusion: • Hemorrhage or lesions larger than 1/3 MCA territory • Contraindications to thrombolysis
Intervention	TNK 0.25mg/kg IV bolus (max 25mg)	
Comparator	TPA 0.9mg/kg (10% bolus then 90% over 1 h; max 90mg)	
Outcomes	1° = substantial reperfusion (restoration of 50% blood flow or thrombus gone by EVT) 2° = mRS 0-1 @ 90d, median mRS @ 90d, symptomatic intracranial hemorrhage (sICH)	

N Engl J Med 2018;378:1573-82.

RESULTS

	NOR-TEST (Lancet Neurol 2017;16:781-88)	**EXTEND-IA TNK (N Engl J Med 2018;378:1573-82)**
Patients	N=1100 71yo Norwegian about 2h from stroke onset; NIHSS 4	N=202 71 yo Australian with LVO and undergoing EVT NIHSS 17
Comparison	TNK 0.4mg/kg vs. TPA	TNK 0.25mg/kg vs. TPA
Substantial reperfusion		22 vs. 10% (p=0.03)
mRS 0-1 @ 90d	64% vs. 63% (p=0.52)	51 vs. 43% (p=0.2)
Median mRS @ 90d		2 vs. 3 (p=0.04)
sICH	3% vs. 2% (p=0.7)	1 vs. 1%

EXTEND-IA TNK PART 2

Design	**PROBE, MC, Superiority**	
Patients	Inclusion: • Clinical signs of acute stroke < 4.5h • >18 yo • Independent • Large vessel occlusion and eligible for EVT	Exclusion: • Hemorrhage or lesions larger than 1/3 MCA territory • Contraindications to thrombolysis
Intervention	TNK 0.4mg/kg IV bolus (max 40mg)	
Comparator	TNK 0.25mg/kg IV bolus (max 25mg)	
Outcomes	1° = substantial reperfusion (restoration of 50% blood flow or thrombus gone by EVT) 2° = mRS 0-1 @ 90d, median mRS @ 90d, symptomatic intracranial hemorrhage (sICH)	

JAMA 2020;323:1257-65.

RESULTS

	NOR-TEST (Lancet Neurol 2017;16:781-88)	**EXTEND-IA TNK (N Engl J Med 2018;378:1573-82)**	**EXTEND-IA TNK p2 (JAMA 2020;323:1257-65)**
Patients	N=1100 71yo Norwegian about 2h from stroke onset; NIHSS 4	N=202 71 yo Australian with LVO and undergoing EVT NIHSS 17	N=300 72 yo Australian with LVO and undergoing EVT NIHSS 16-17
Comparison	TNK 0.4mg/kg vs. TPA	TNK 0.25mg/kg vs. TPA	TNK 0.4mg/kg vs. 0.25mg/kg
Substantial reperfusion		22 vs. 10% (p=0.03)	19.3 vs. 19.3% (p=0.89)
mRS 0-1 @ 90d	64% vs. 63% (p=0.52)	51 vs. 43% (p=0.2)	49 vs. 49% (p=0.69)
Median mRS @ 90d		2 vs. 3 (p=0.04)	2 vs. 2 (p=0.73)
sICH	3% vs. 2% (p=0.7)	1 vs. 1%	4.7 vs. 1.3% (p=0.12)

TNK TRIALS IN THE PIPELINE

Trial	Design	Patients	Intervention	
TASTE	MC, PROBE	Goal n = 1024 ≤ 4.5h from onset with favourable imaging criteria	TNK 0.25 mg/kg TPA 0.9 mg/kg	Ongoing: estimated completion Dec 2018 (only 186 subjects enrolled to date)
ATTEST-2	MC, P, R, O-L	Goal N = 1870 ≤ 4.5h from onset	TNK 0.25 mg/kg TPA 0.9 mg/kg	Ongoing: estimated completion August 2019
TEMPO 2	MC, PROBE	Goal n = 1274 <12 hours from onset TIA or "minor stroke"	TNK 0.25 mg/kg vs. Standard of care antiplatelets	Ongoing: estimated completion Dec 2023

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TNK TRIALS IN THE PIPELINE

Trial	Design	Patients	Intervention	
TWIST	MC, PROBE	Goal n = 500 wake up strokes ≤ 4.5h from awakening with symptoms	TNK 0.25 mg/kg Standard care	Ongoing: estimated completion Dec 2022
AcT	MC, PROBE	Goal n=1600 ≤ 4.5h from symptom onset	TNK 0.25 mg/kg TPA 0.9 mg/kg	Ongoing: estimated completion Dec 2022
NOR-TEST-2	MC, PROBE	Goal n = 1342 ≤ 4.5h from symptom onset or awakening with symptoms	TNK 0.4 mg/kg TPA 0.9 mg/kg	Ongoing: estimated completion May 2023

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SUMMARY OF TNK LITERATURE TO DATE

- 0.4mg/kg dose not superior to TPA in minor stroke population (median NIHSS 4), and has higher ICH rates than the 0.25mg/kg dose
- 0.25mg/kg dose was superior to TPA at reperfusion of LVO, with similar ICH rates
- Advantages of bolus administration felt to be clinically relevant

THE BOTTOM LINE

- Acute stroke therapy is all about facilitating reperfusion in patients whose brain tissue is not yet irreversibly ischemic

THINGS TO COME:

- Shift from time based to tissue based therapy
  - Facilitated by advanced imaging techniques
  - At this point does not negate time-frames, but hopes to include more patients that may benefit from stroke therapy
  - Potential expansion of time window in highly selected patients under the recommendation of a stroke specialist

- Role of TNK
  - Potential alternative to TPA
  - Facilitate transport ("drip and ship"), facilitate imaging, minimize nursing interaction
  - Proposed safety advantages due to fibrin specificity – yet to be proven in stroke

- Role of low dose TPA
  - Not likely to gain much utilization without further evidence
  - Likely to be overshadowed by attempting to ↓ ICH risk through patient selection and imaging criteria

RECAP OF THE CASE

- 90yo, LVO, wake-up stroke (at worst 9h50min from onset; at best 3h50min from onset to diagnosis at NRGH)

- Therapeutic alternatives
  - Assess for thrombolytic therapy
    - Current state – no thrombolytic
    - Future state – MRI completed rather than CTA, if eligible, TNK then ship to Victoria General
  - Assess for EVT
    - Ship straight to Victoria General for EVT assessment
    - Likely repeat CTA or MRI upon arrival

QUESTIONS

- Reminder of learning objectives:
  - Identify the limitations of the historical thrombolytic therapy literature and recommendations
  - Summarize the paradigm shift from *time based* treatment to *tissue based* treatment
  - List the new strategies of thrombolytic therapy currently under investigation in attempts to optimize acute stroke management