# Assoc. Prof. Deidre Ann De Silva

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# IV thrombolysis and stroke care: Lessons, challenges & opportunities

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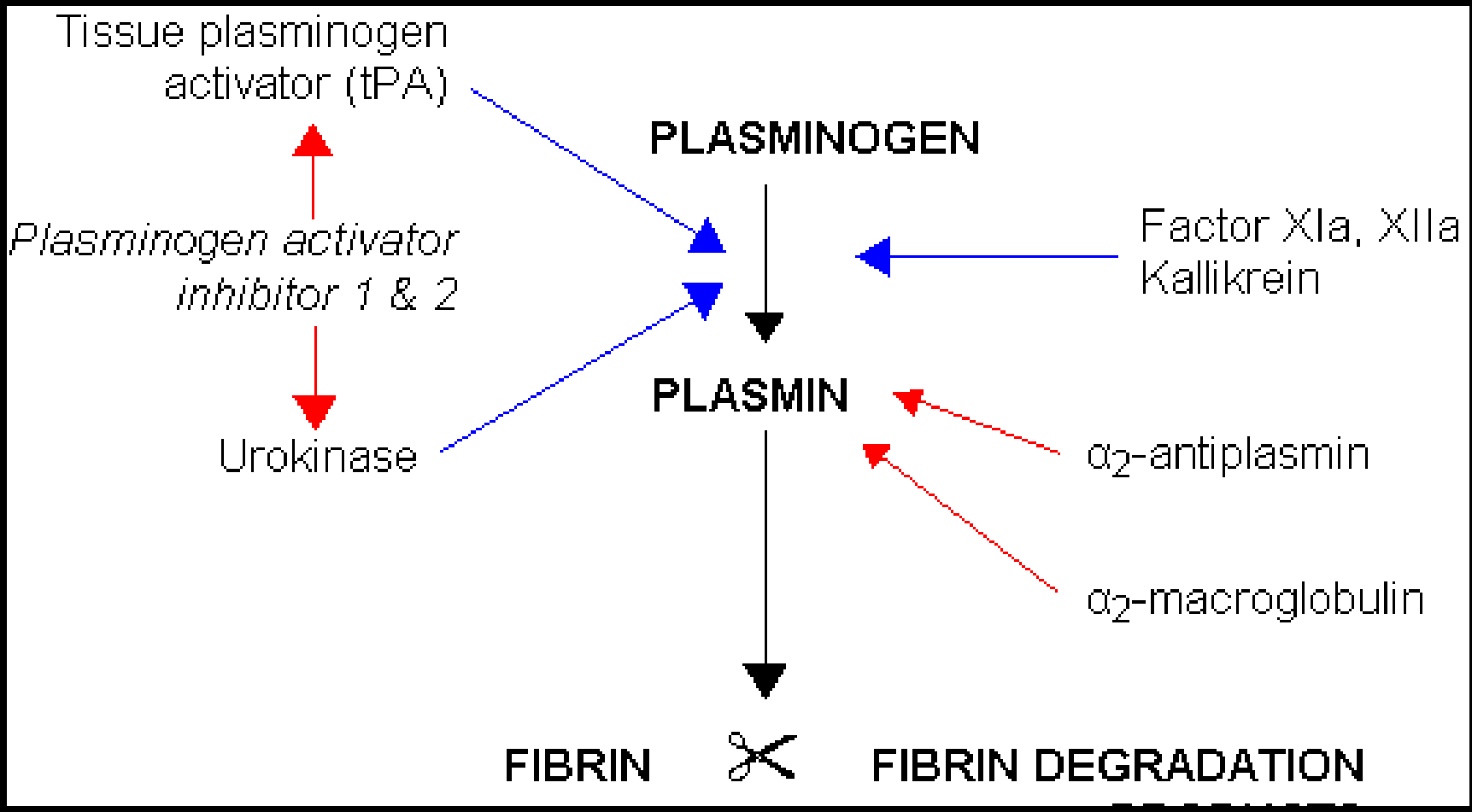
# OUTLINE

- Part 1: Concept of thrombolysis
- Part 2: Unselected patients in the early time window
- Part 3: Selection of patients in wider time window
- Part 4: Beyond IV alteplase
- Part 5: Lessons
- Part 6: Challenges
- Part 7: Opportunities

# Part 1: Concept of thrombolysis

## Fibrinolytics: Tissue plasminogen activator (tPA)

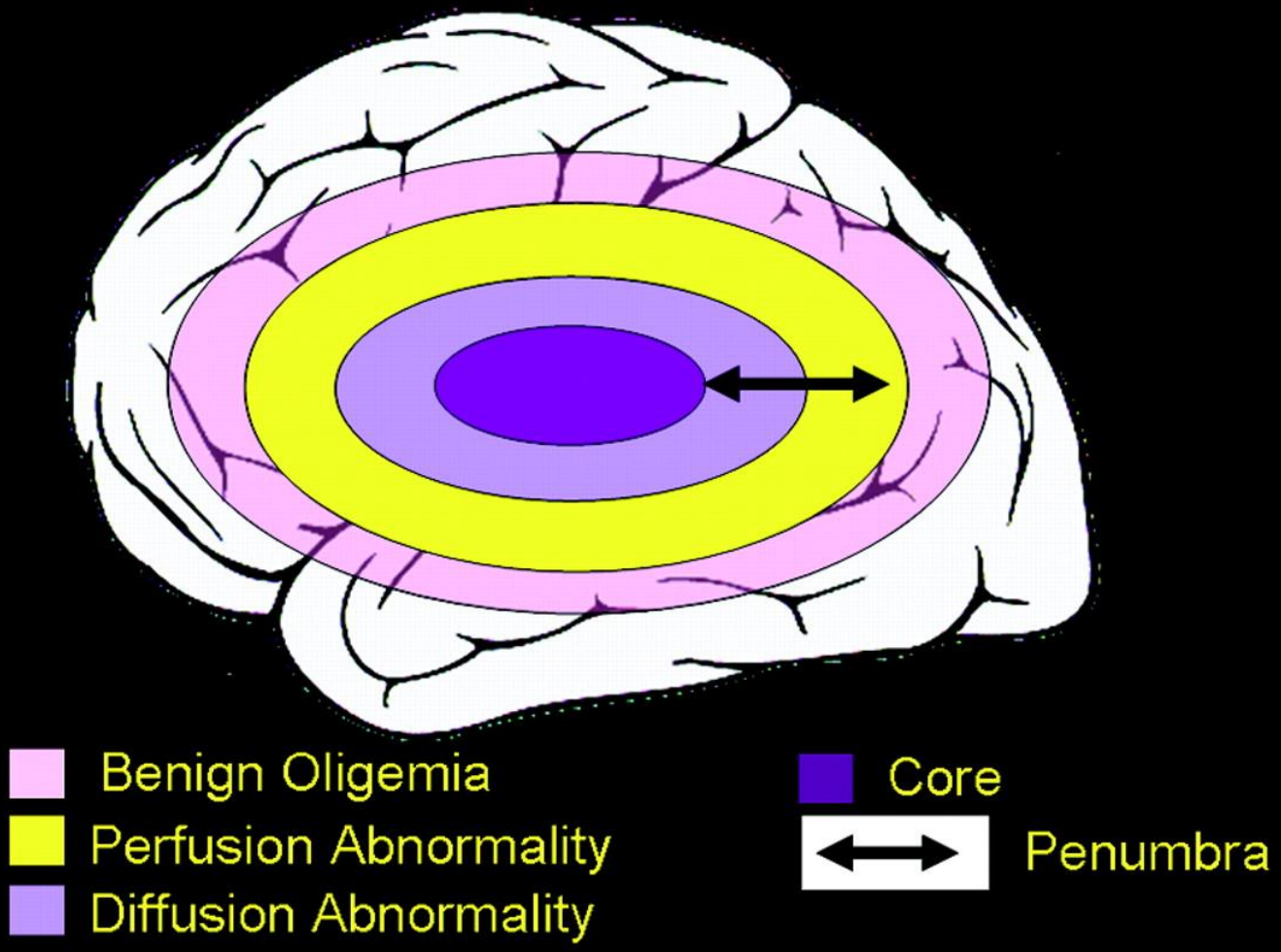


# Fibrinolytics

| Agent | Half-life (min | Fibrin selectivity | PAI-1 inhibition |
|---|---|---|---|
| Urokinase | 15 | - | +++ |
| Alteplase | 4-8 | ++ | +++ |
| Staphylokinase | 6 | --- | - |
| Monteplase | 23 | +/- | +++ |
| Pamiteplase | 30-47 | ++ | +++ |
| Lanoteplase | 23-37 | + | - |
| Reteplase | 14-18 | + | ++ |
| Tenecteplase | 11-20 | +++ | - |
| Desmoteplase | 138 | +++++ | ? |

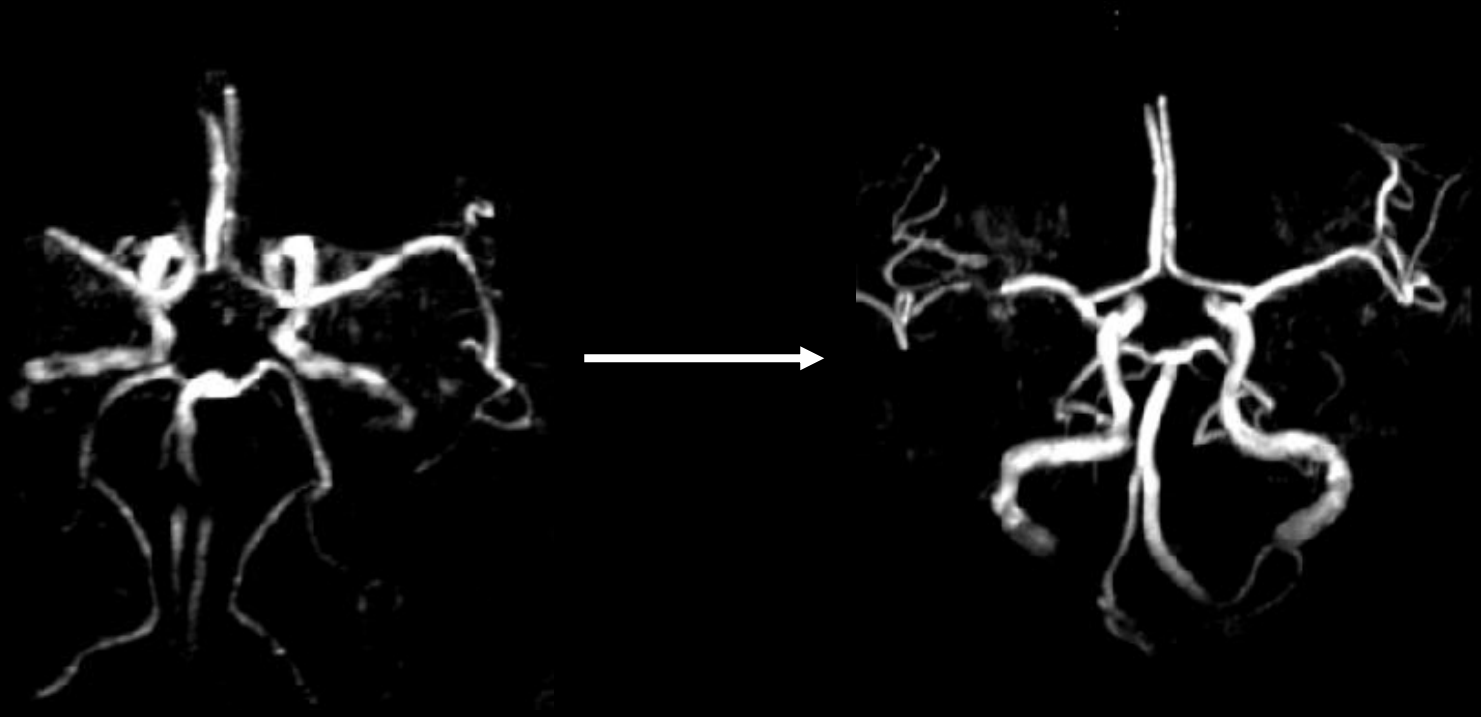
From the J of Stroke

# Ischemic Penumbra

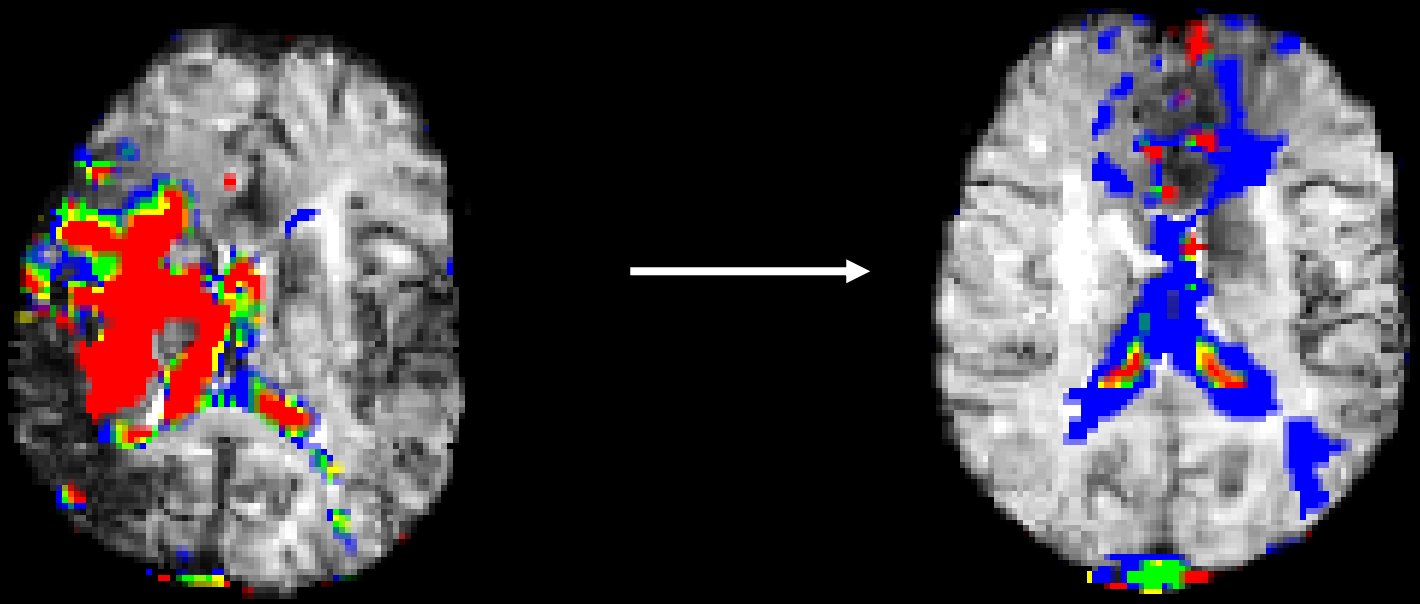



Kidwell et al

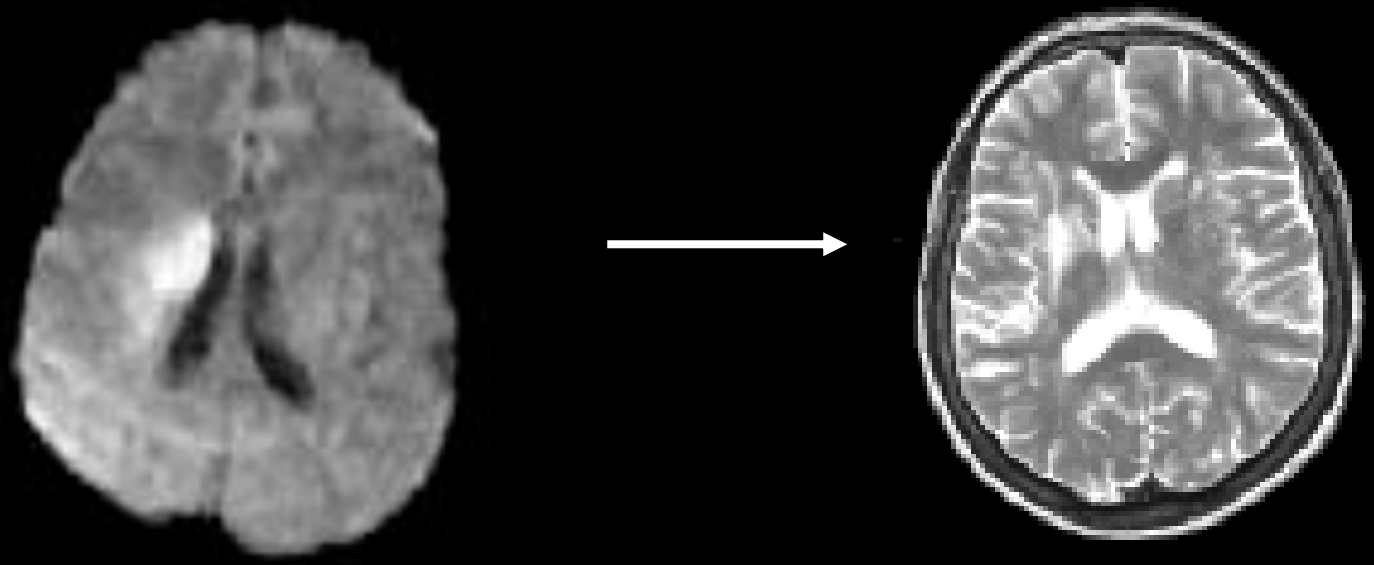
# Recanalization of arterial occlusion



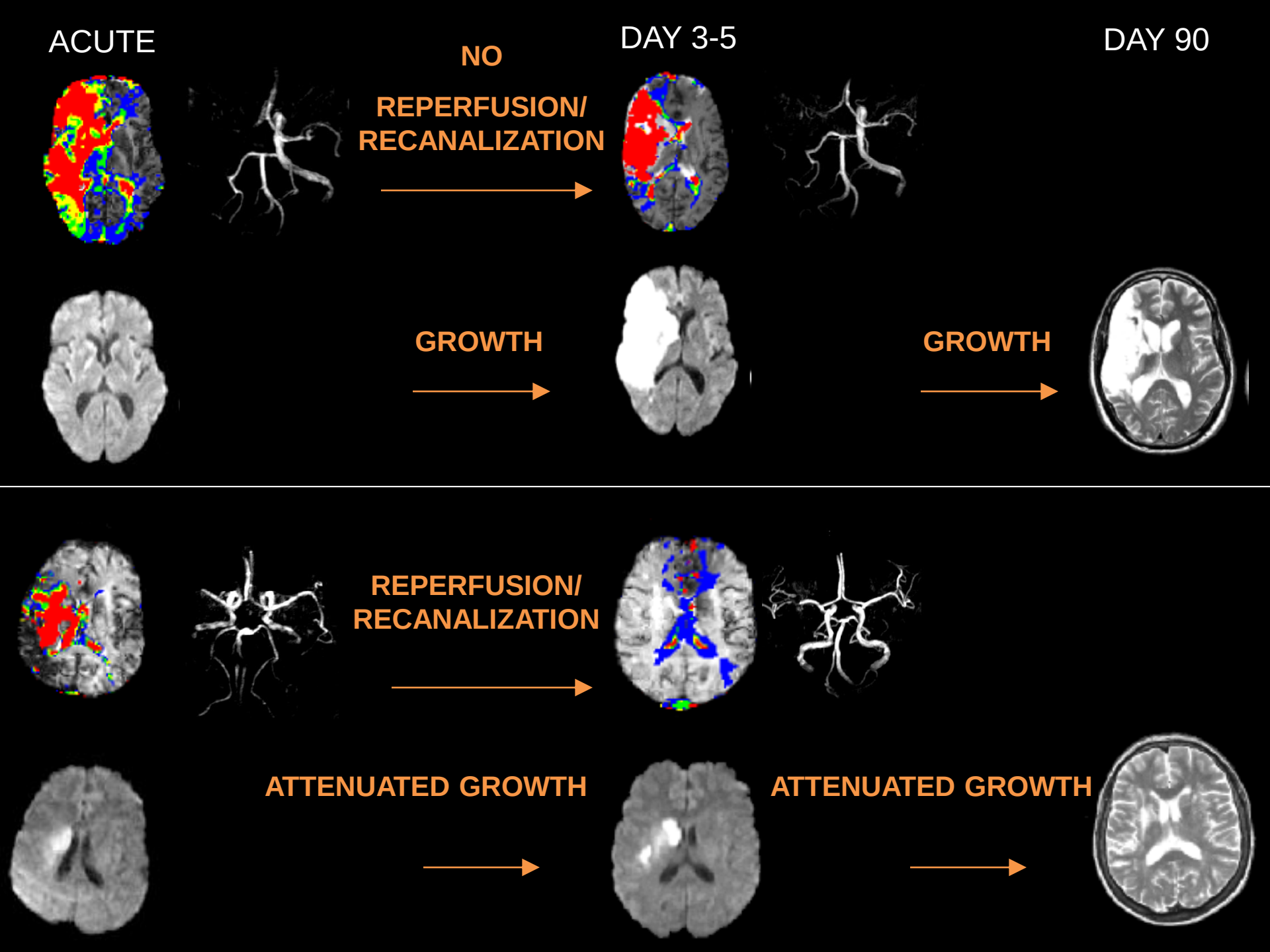
# Reperfusion of salvageable tissue



# Attenuation of Infarct Growth

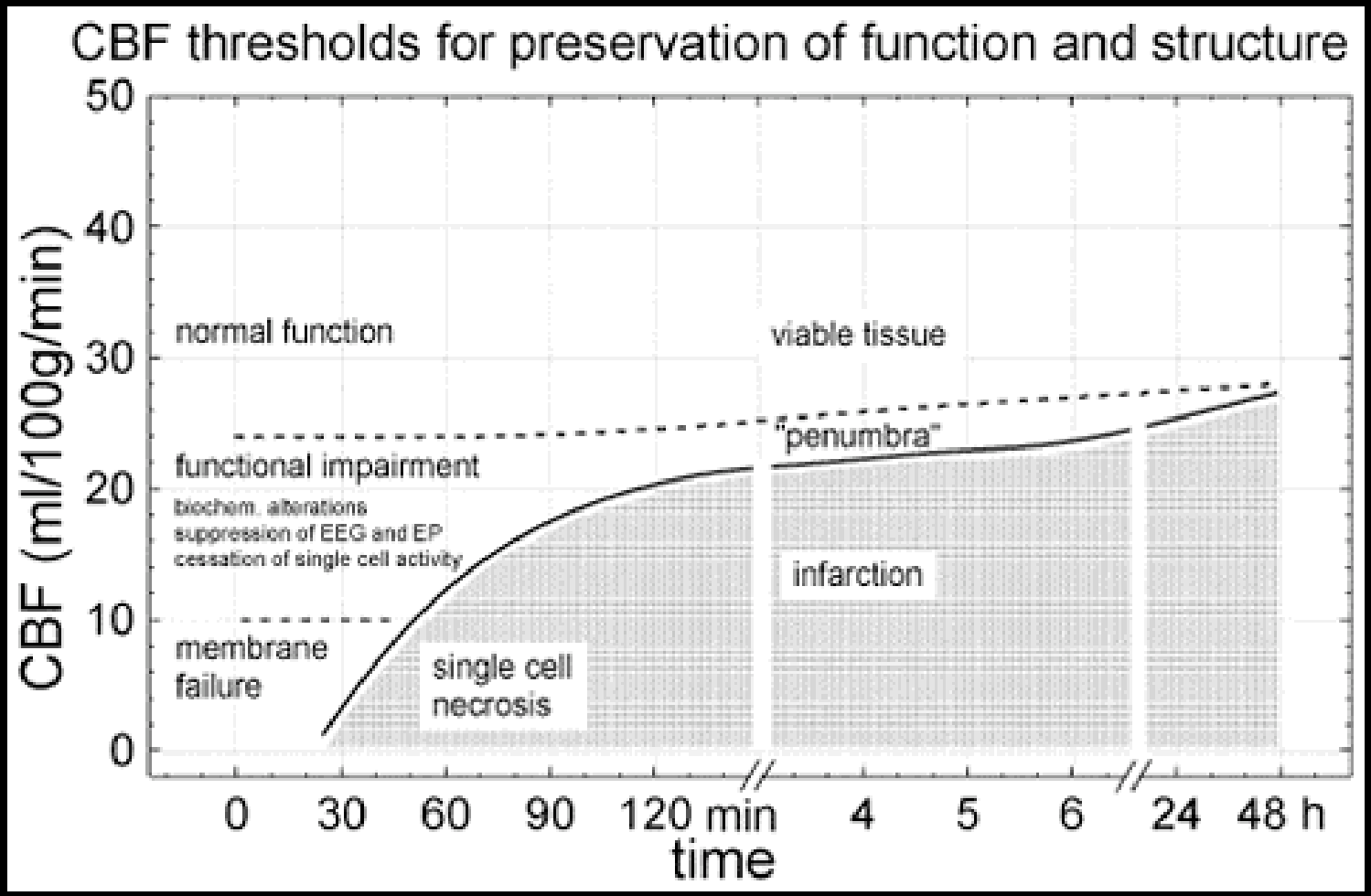


# Improved neurological & functional outcomes


ACUTE
DAY 3-5
DAY 90
NO
REPERFUSION/
RECANALIZATION
GROWTH
GROWTH
REPERFUSION/
RECANALIZATION
ATTENUATED GROWTH
ATTENUATED GROWTH

# TIME IS BRAIN

*58 million neurons die for each hour that stroke goes untreated (Saver)*



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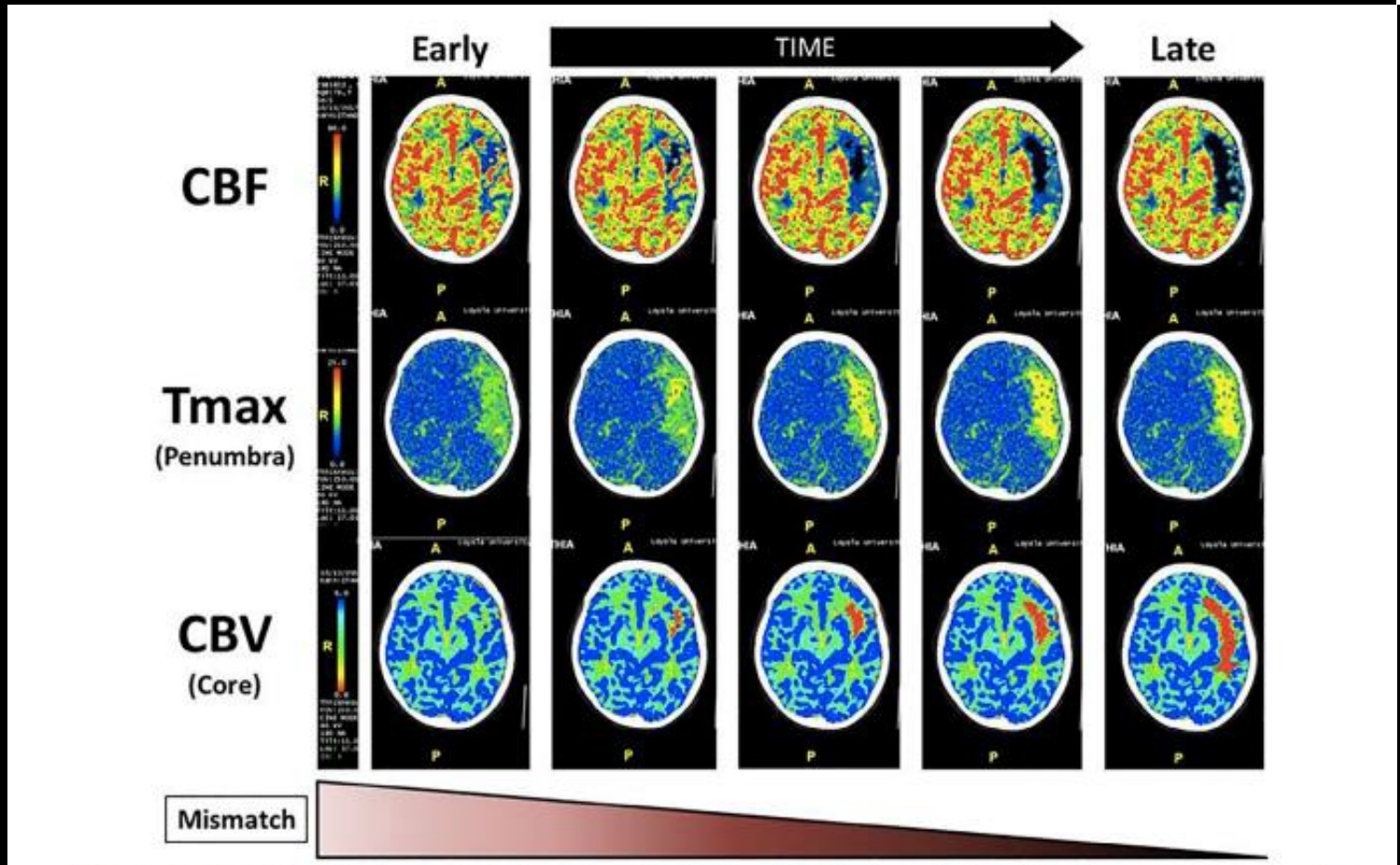
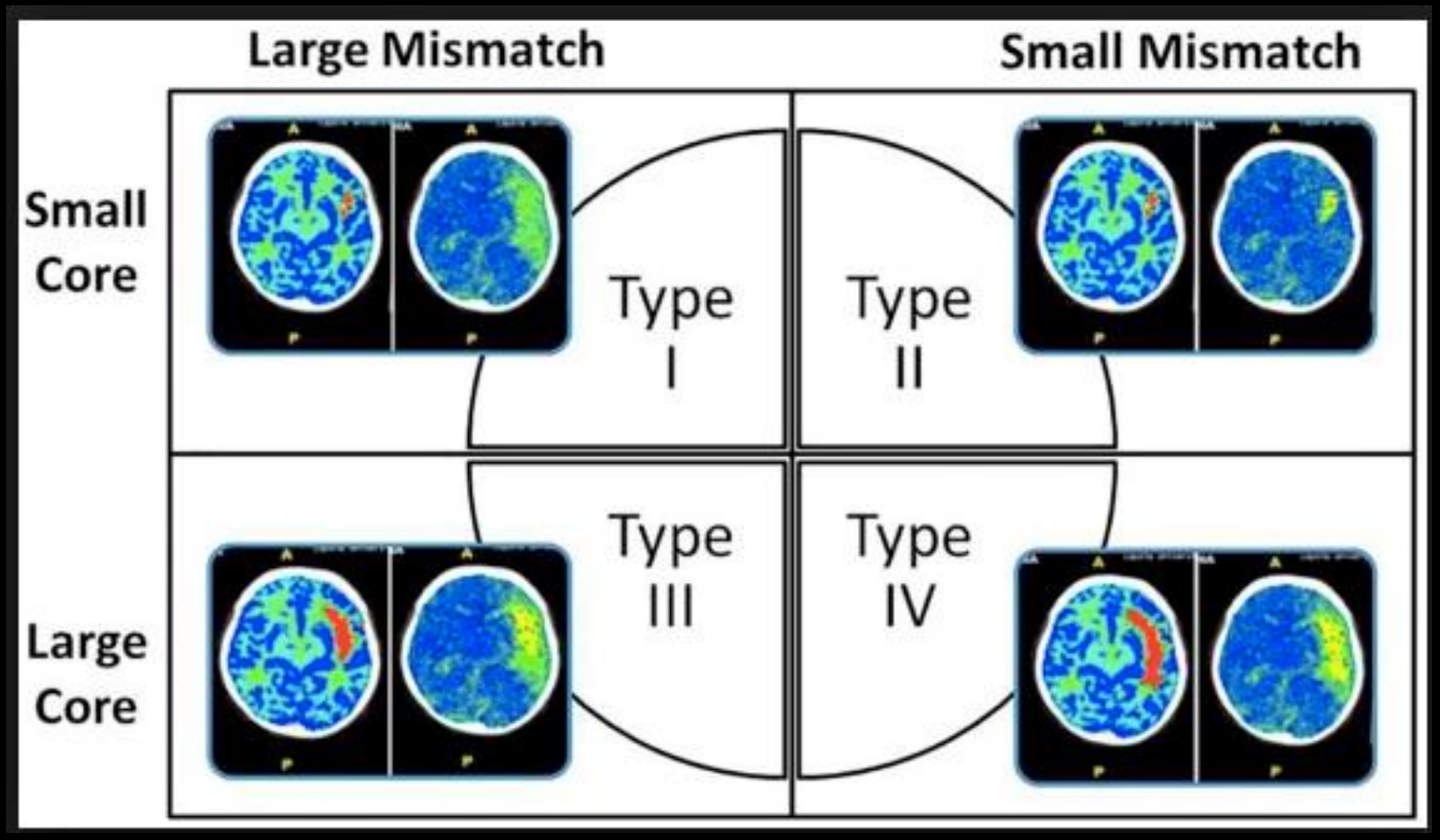


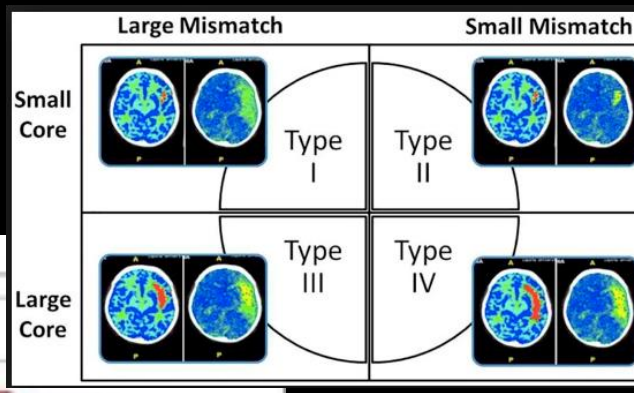

**Figure 1.** *Artistic rendition of the classic understanding of the relationship between the "ischemic core" and the "ischemic penumbra" volumes along the time continuum based on CTP perfusion maps. Early after onset, the penumbra rapidly achieves a maximum volume, whereas the core is minimal, resulting in a pronounced "ischemic mismatch." Later, as time elapses, the continued blood flow insufficiency leads to progressive expansion of the core, with reciprocal reduction of the mismatch. Concurrently, the intensity changes progressively more evident in the penumbra mirror the core expansion and,*

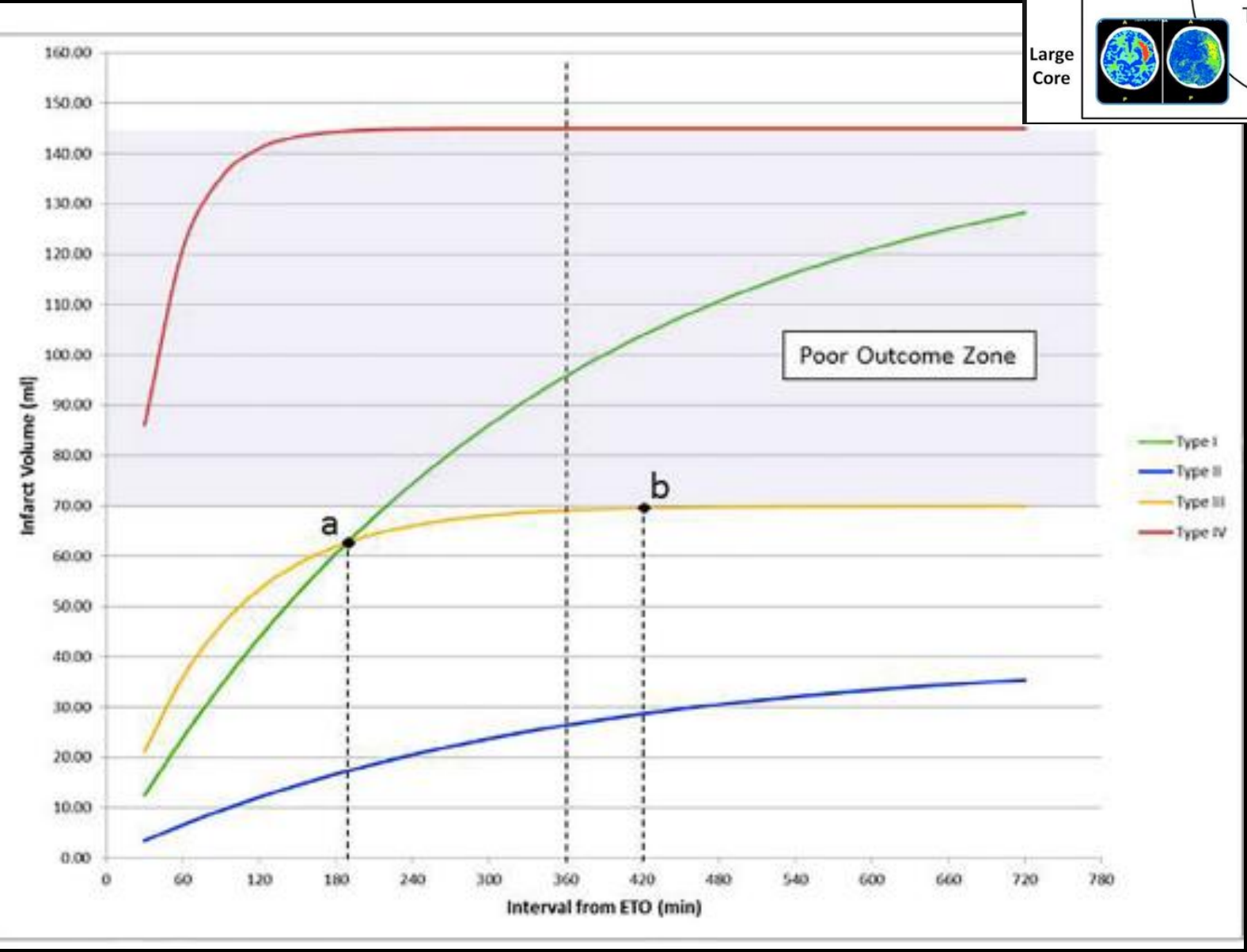
# Stroke theory of relativity




Gomez et al

# Stroke theory of relativity- by modeling




Gomez et al

# Part 2: Unselected patients in early window RCT EVIDENCE <3 hours

- BENEFIT
  - mRS 0-1 at 3 months 39% tPA vs 26% placebo
  - OR 1.7; 30% RRR; 13% ARR; NNT 8
  - Improvement of mRS by 1 point NNT 3

- RISK OF sICH = haemorrhage on 24 h CT + clinical suspicion of haemorrhage or decline in neurological status
  - Any sICH 0.6% in placebo arm; 6.6% in tPA arm
  - Number needed to harm: mRS 4-6 due to sICH = 126

- Survival = no change

NINDS, NEJM 1995

Saver, Arch Neurol 2004

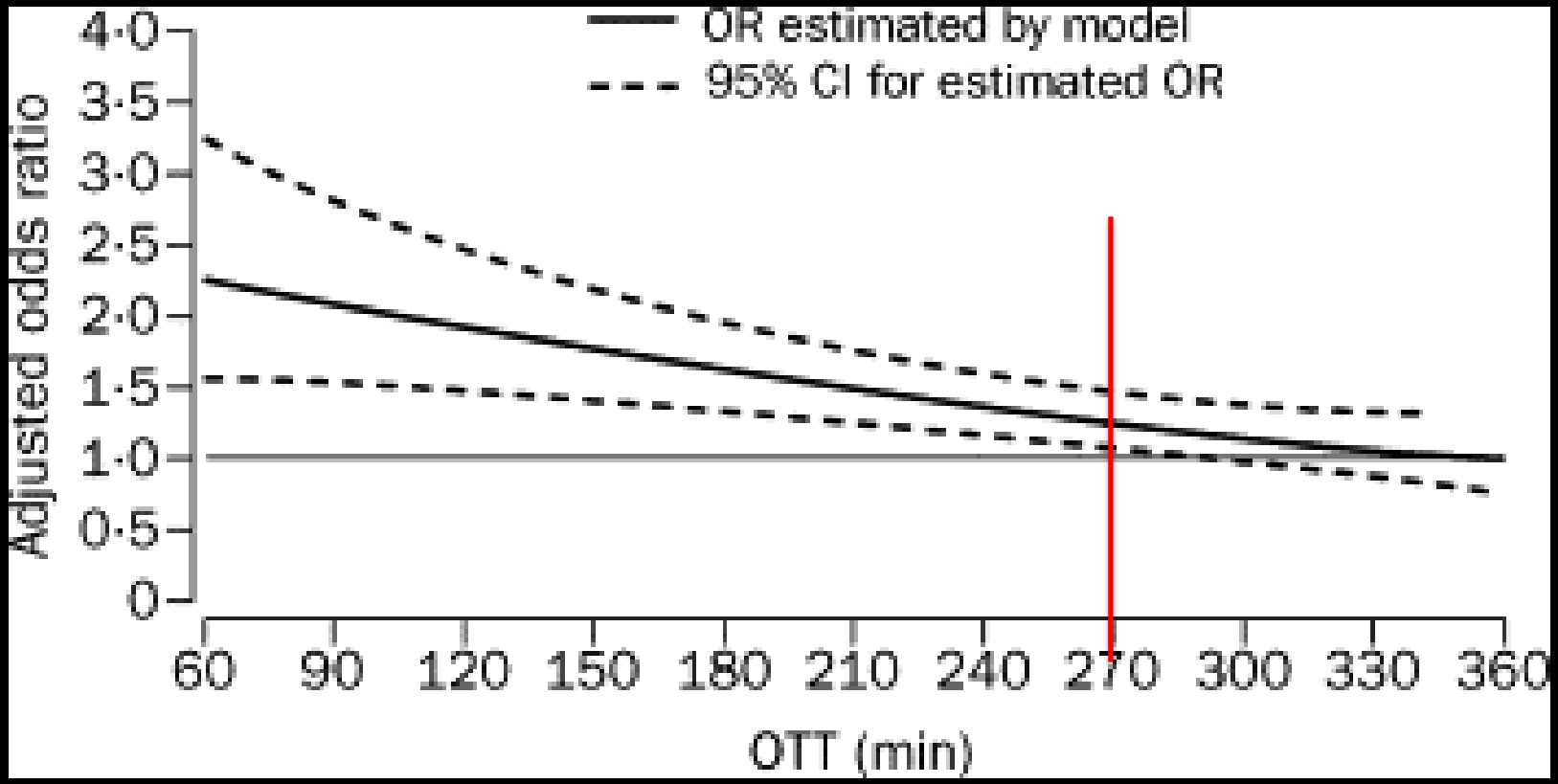
# RCT 3 to 4.5 hours

- BENEFIT At 3 months, mRS 0-1
  - tPA 52.4%, Placebo 45.2%
  - ARR 7.2%, NNT 14
  - OR 1.34 (1.02- 1.76)
- RISKS
  - sICH 7.9% vs 3.5%, p=0.006
- SURVIVAL
  - No change

ECASS III

Hacke, NEJM, 2008

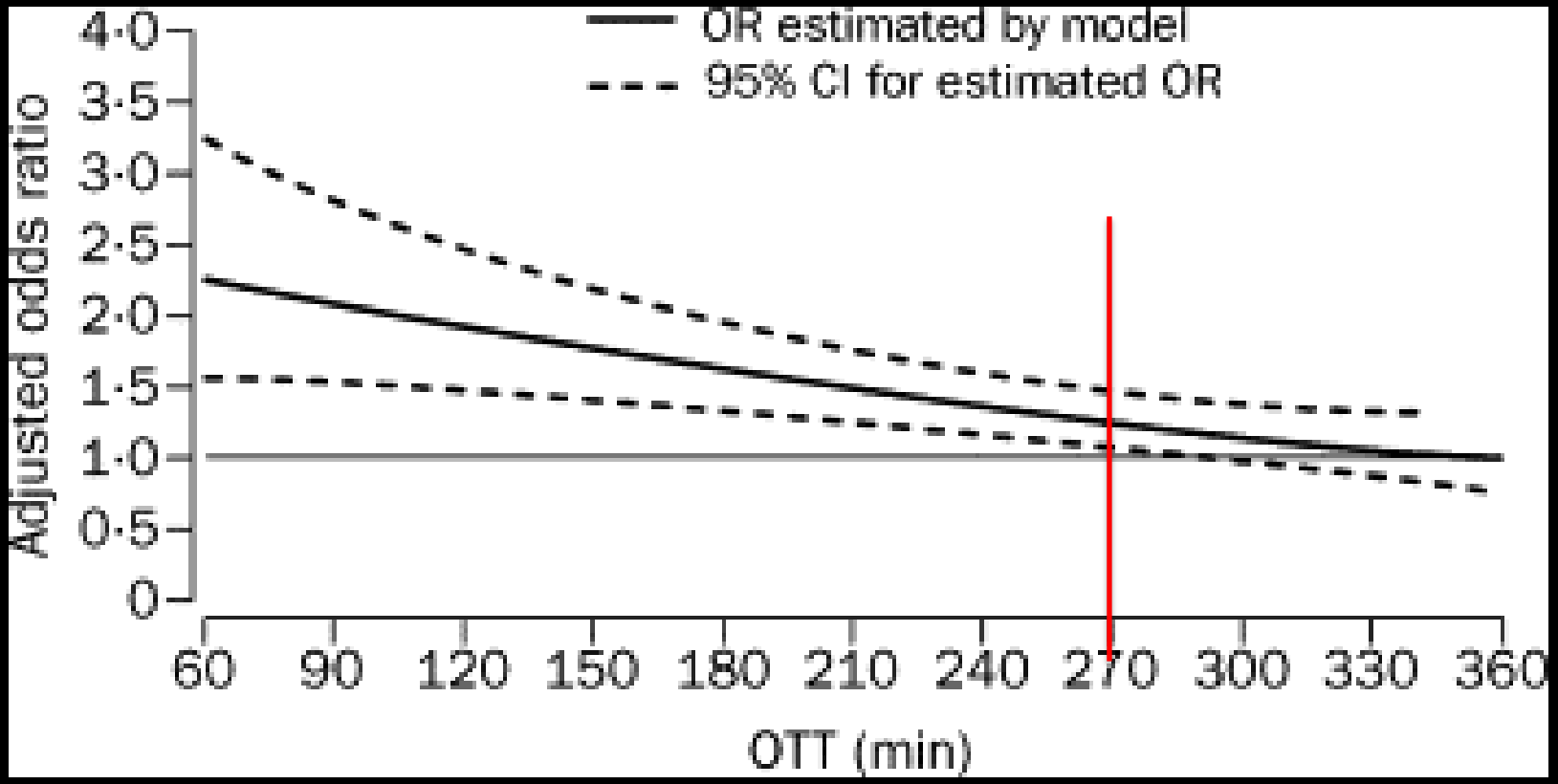
# Earlier treatment is more effective




- At 3 months, OR for good outcome
  - 0-90 2.2 (1.8 to 4.5)
  - 91-180 1.6 (1.1 to 2.2)
  - 181-270 1.4 (1.1 to 1.9)
  - 271-360 1.2 (0.9 to 1.5)

Hacke, Lancet 2004

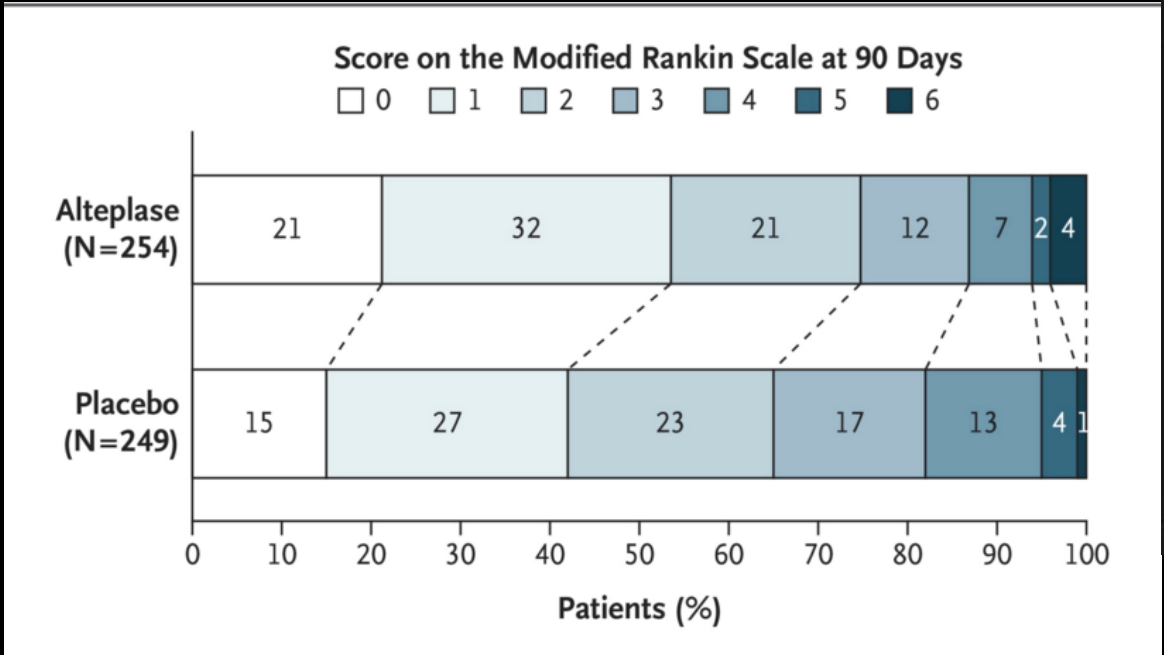
# Part 3: Selected patients in wider window




- Unknown onset: Wake Up
- Increased benefit, lower risk: Penumbral selection

# Unknown onset: Wake-up trial

- Inclusion
  - Unknown onset time
  - DWI: FLAIR mismatch
  - Within 4.5h of discovery
- IV tPA or placebo



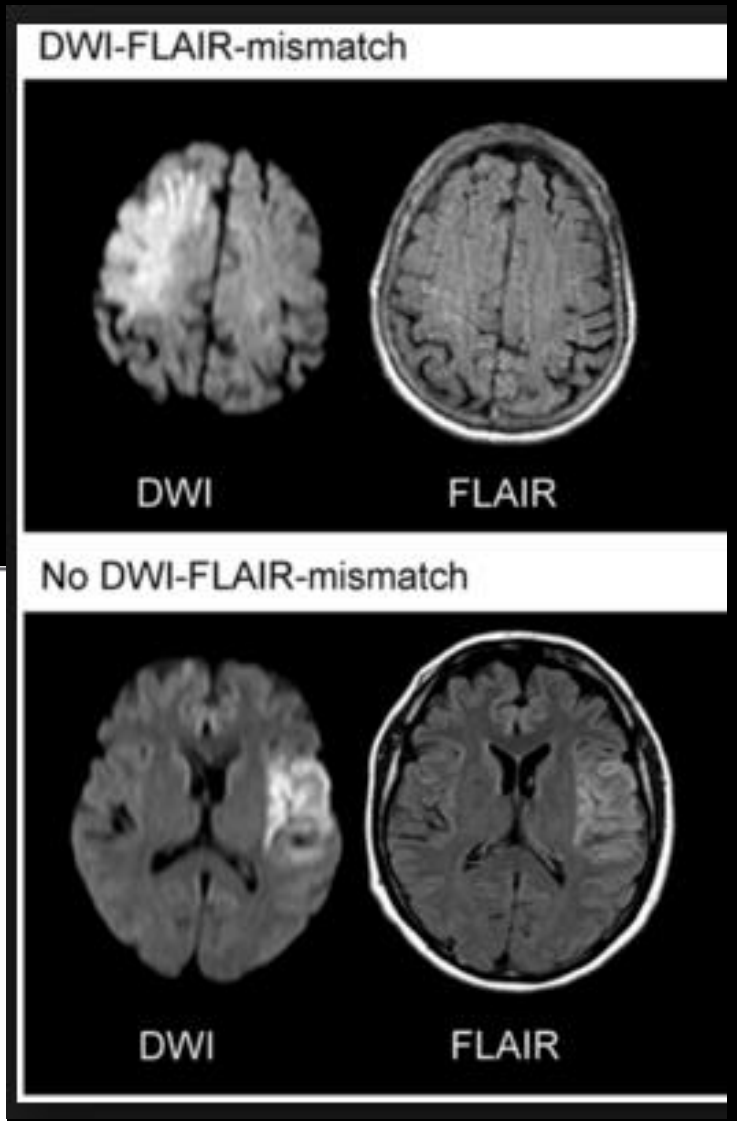



**Table 2.** Primary and Secondary Efficacy Outcomes (Intention-to-Treat Population).*

mRS 0-1

| Outcome | Alteplase Group (N=254) | Placebo Group (N=249) | Effect Variable | Adjusted Value (95% CI)† | P Value |
|---|---|---|---|---|---|
| **Primary efficacy end point** | | | | | |
| Favorable outcome at 90 days — no./total no. (%)‡ | 131/246 (53.3) | 102/244 (41.8) | Odds ratio | 1.61 (1.09 to 2.36) | 0.02 |

**Table 3.** Safety Outcomes.

| Outcome | Alteplase Group (N=251) | Placebo Group (N=244) | Adjusted Odds Ratio (95% CI)* | P Value |
|---|---|---|---|---|
| | *no. (%)* | | | |
| **Primary†** | | | | |
| Death or dependency at 90 days | 33 (13.5) | 44 (18.3) | 0.68 (0.39–1.18) | 0.17 |
| Death at 90 days | 10 (4.1) | 3 (1.2) | 3.38 (0.92–12.52) | 0.07 |
| **Secondary** | | | | |
| Symptomatic intracranial hemorrhage | | | | |
| As defined in SITS-MOST‡ | 5 (2.0) | 1 (0.4) | 4.95 (0.57–42.87) | 0.15 |

# Penumbral selection: Extend trial

- Inclusion
  - Within 4.5 to 9 h of onset or awakening
    - if within 9 h from midpoint of sleep
  - Favourable imaging pattern
    - using MRI or CT Tmax >6 sec delay & MRI DWI and CBF
    - Penumbral mismatch
      - "hypo-perfusion to core" volume ratio > 1.2, and
      - absolute difference > 10ml
      - An infarct core lesion <=70ml
- IV tPA vs placebo
- Stopped: clinical equipoise due to another trial

# EXTEND trial: longer window, penumbral selection

- Primary outcome mRS 0-2
  - 35.4% vs 29.5% (adjusted risk ratio, 1.44; 95% CI 1.01 to 2.06; P=0.04)
- Ordinal shift of MRS no significant difference
- sICH 6.2% vs 09% adjusted risk ratio, 7.22; 95% CI, 0.97 to 53.5, p=0.05

# Pooled Penumbral data - EXTEND, ECASS4-EXTEND, EPITHET

- 4.5 to 9 h from onset or wake up

- Reprocessed imaging
- Mismatch pattern using CTP or MRI PWI
- Mismatch status
  - mismatch ratio greater than 1·2
  - mismatch volume greater than 10mL

NEJM 2019

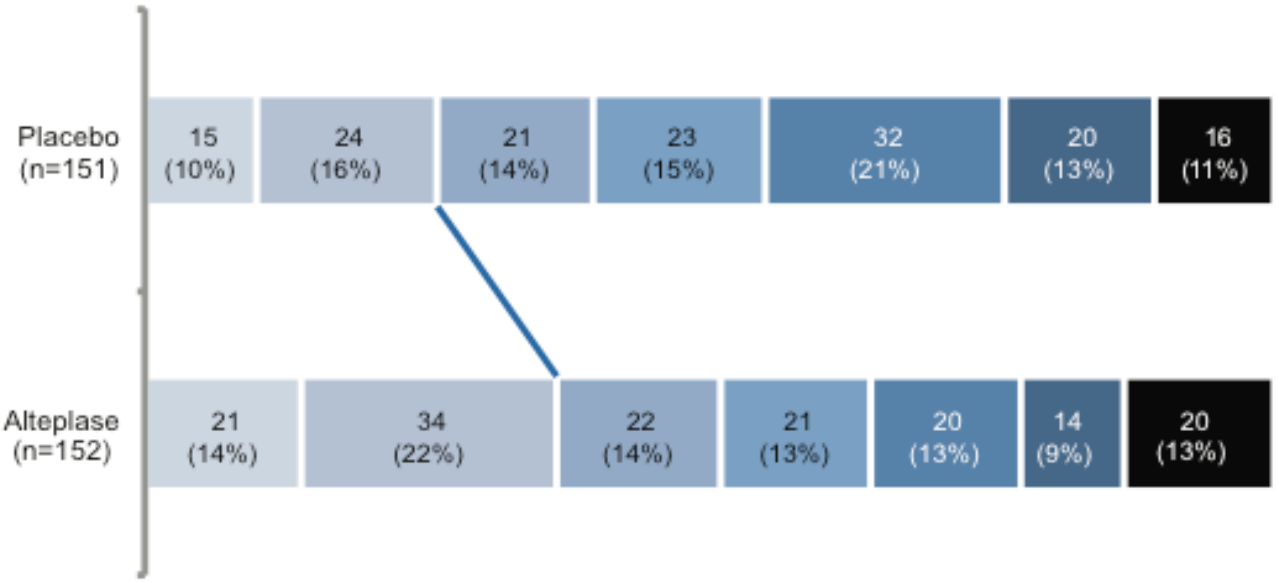
**TABLE 2. Study outcomes in all patients**

| Outcome | Placebo (n=201) | IV-alteplase (n=213) | Effect size* (95%CI) | p-value |
|---|---|---|---|---|
| **Primary outcome** Excellent outcome (mRS0-1) at 90 days | 58/199 (29%) | 76/211 (36%) | 1·86 (1·15-2·99) | 0·01 |
| **Secondary Outcomes** Functional outcome at 90 days (Modified Rankin Scale – mRS): | | | | |
| Functional improvement† | | | 1·60 (1·12-2·27) | 0·009 |
| Functional independence (mRS 0-2) | 87/199 (44%) | 103/211 (49%) | 1·74 (1·08-2·81) | 0·02 |
| Early neurological improvement‡ | 31/197 (16%) | 58/206 (28%) | 2·54 (1·51-4·27) | <0·0001 |
| **Safety** | | | | |
| Death (90 days) | 18/201 (9%) | 29/213 (14%) | 1·55 (0·81-2·97) | 0·19 |
| SICH§ (36 hours) | 1/201 (0·5%) | 10/213 (4·7%) | 9·70 (1·23-76·55) | 0·03 |

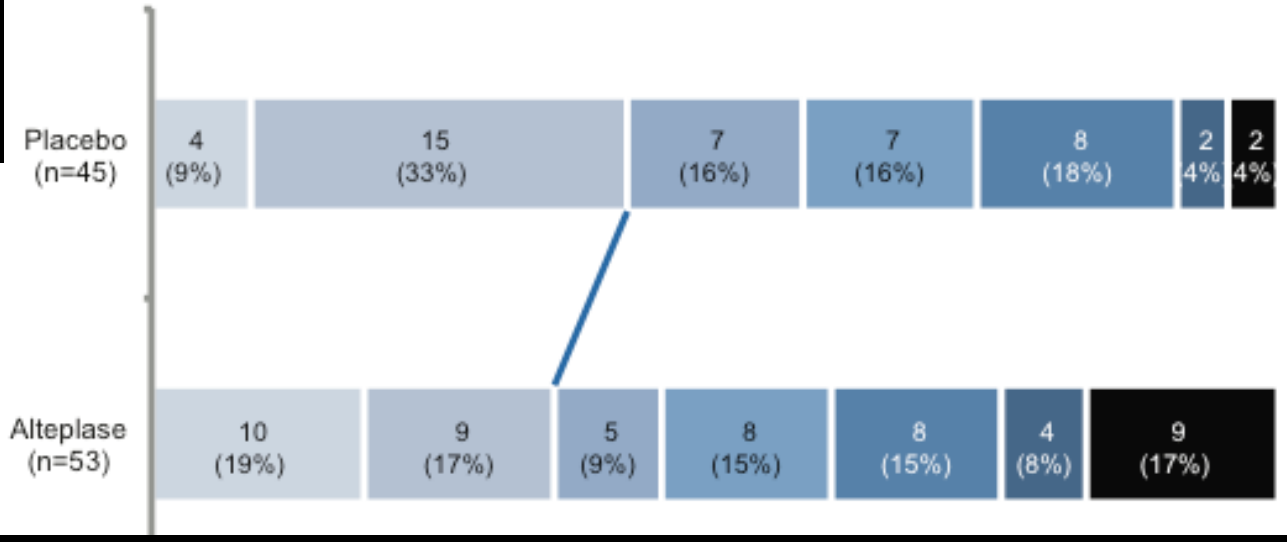
**TABLE 4. Study outcomes in patients with automated perfusion mismatch**

| Outcome | Placebo (n=152) | IV-alteplase (n=152) | Effect size (95%CI)* | p-value |
|---|---|---|---|---|
| **Primary outcome** Excellent outcome (mRS0-1) at 90 days | 39/151 (26%) | 55/152 (36%) | 2·12 (1·20-3·74) | 0·009 |
| **Secondary Outcomes** Functional outcome at 90 days (Modified Rankin Scale – mRS): | | | | |
| Functional improvement† | | | 1·58 (1·05-2·36) | 0·03 |
| Functional independence (mRS0-2) | 60/151 (40%) | 77/152 (51%) | 2·22 (1·25-3·94) | 0·006 |
| Early neurological improvement‡ | 26/152 (17%) | 44/148 (30%) | 2·26 (1·26-4·03) | 0·006 |
| **Safety** | | | | |
| Death (90 days) | 16/152 (11%) | 20/152 (13%) | 1·28 (0·60-2·73) | 0·52 |
| SICH§ (36 hours) | 1/151 (1%) | 7/152 (5%) | 7·30 (0·88-60·35) | 0·06 |

MISMATCH on automated assessment




NO MISMATCH on automated assessment



# What to do - with these data?

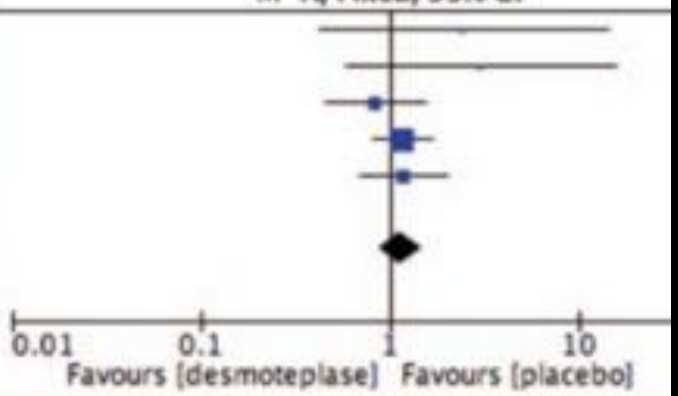
- Within 4.5 h
  - CT alone can suffice
  - If have CTP/ MR perfusion: may provide additional information but not essential
  - CTA to determine possibility of ECR
- Unknown onset
  - Choice
    - 1) MRI to look for DWI: FLAIR mismatch to determine age of infarction
    - 2) CTP/ MR perfusion to look for penumbral pattern
- Known onset 4.5 to 9h
  - CTP/ MR perfusion to look for penumbral pattern

# Part 4: Beyond alteplase: Demise of desmoteplase

| Study or Subgroup | Experimental Events | Experimental Total | Control Events | Control Total | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| DEDAS 2003 | 13 | 29 | 2 | 8 | 1.6% | 2.44 [0.42, 14.16] |
| DIAS 2001 | 18 | 45 | 2 | 11 | 1.8% | 3.00 [0.58, 15.53] |
| DIAS-2 2005 | 51 | 123 | 29 | 63 | 21.4% | 0.83 [0.45, 1.53] |
| DIAS-3 2009 | 108 | 236 | 100 | 237 | 51.6% | 1.16 [0.80, 1.66] |
| DIAS-4 2014 | 40 | 124 | 37 | 128 | 23.5% | 1.17 [0.68, 2.00] |
| **Total (95% CI)** | | **557** | | **447** | **100.0%** | **1.14 [0.88, 1.49]** |
| Total events | 230 | | 170 | | | |

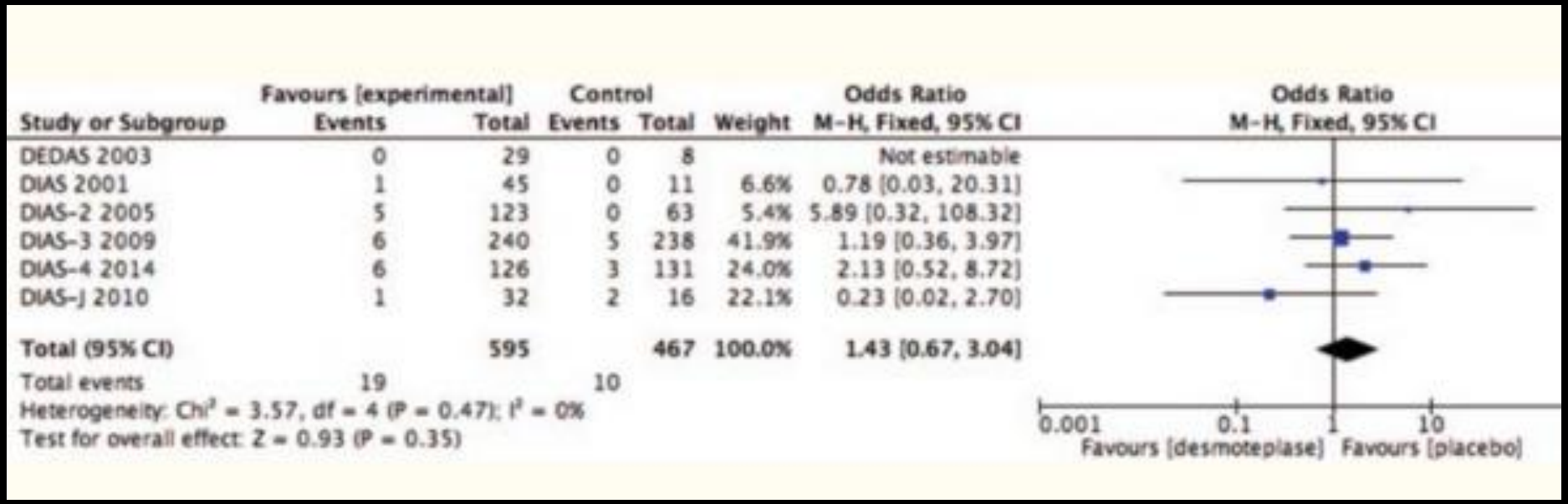
Heterogeneity: $Chi^2 = 3.10$, $df = 4$ ($P = 0.54$); $I^2 = 0\%$

Test for overall effect: $Z = 1.01$ ($P = 0.31$)




FAVOURABLE OUTCOME

# Demise of desmoteplase



| Study or Subgroup | Favours [experimental] Events | Total | Control Events | Total | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| DEDAS 2003 | 0 | 29 | 0 | 8 | | Not estimable |
| DIAS 2001 | 1 | 45 | 0 | 11 | 6.6% | 0.78 [0.03, 20.31] |
| DIAS-2 2005 | 5 | 123 | 0 | 63 | 5.4% | 5.89 [0.32, 108.32] |
| DIAS-3 2009 | 6 | 240 | 5 | 238 | 41.9% | 1.19 [0.36, 3.97] |
| DIAS-4 2014 | 6 | 126 | 3 | 131 | 24.0% | 2.13 [0.52, 8.72] |
| DIAS-J 2010 | 1 | 32 | 2 | 16 | 22.1% | 0.23 [0.02, 2.70] |
| **Total (95% CI)** | | **595** | | **467** | **100.0%** | **1.43 [0.67, 3.04]** |
| Total events | 19 | | 10 | | | |

Heterogeneity: $Chi^2 = 3.57$, $df = 4$ ($P = 0.47$); $I^2 = 0\%$
Test for overall effect: $Z = 0.93$ ($P = 0.35$)



Symptomatic intracerebral haemorrhage (sICH)

# Promise of tenecteplase: Nor test

- Inclusion
  - within 4·5 h of  onset or awakening with symptoms, or
  - eligible for bridging therapy before thrombectomy
- Median NIHSS 4, 18% mimics

- IV tenecteplase 0·4 mg/kg (max 40 mg) vs
- IV alteplase 0·9 mg/kg (max 90 mg)

- 3 mth mRS 0-1
  - 64% vs 63% (odds ratio 1·08, 95% CI 0·84-1·38; p=0·52)
- Mortality same, adverse events similar

# Promise of tenecteplase: EXTEND-IA TNK

- Inclusion
  - IS with LVO planned from thrombectomy
- 0.25 mg/kg tenecteplase vs 0.9 mg/kg alteplase

- Reperfusion >50% of involved territory by time of initial angiogram
  - 22% vs 10% p=0.023

- Ordinal analysis of day 90 mRS
  - cOR 1.7, 95% CI 1.0–2.8, *p* = 0.037

# Promise of tenecteplase: Many ongoing trials

- TEMPO-2
- EXTEND-IA TNK II
- TASTE
- ATTEST-2
- TWIST

# Sonothrombolysis – a no go

- CLOT BUSTER: Phase 3 trial
- IS, within 3 or 4.5 h, IV tPA
- Active US (2MHz pulse wave US for 120 min) vs sham US

- adjusted cOR for mRS improvement
  - 1·05 (95% CI 0·77-1·45; p=0·74)

Lancet Neurology Apr 2019

# Part 5: Lessons:
# In relation to other strategies

| | EVIDENCE for benefit (NNT) | RISKS | Proportion "eligible" |
|---|---|---|---|
| IV tPA | Survival = no diff<br>mRS 0-1 = 8-14<br>mRS shift = 3 | sICH<br>Extracranial hemorrhage<br>Allergy | Estimated 40-50% |
| Stroke Unit | Survival = 22<br>Independence = 6 | Nil | 100% |

# Do not waste the benefit

- Ensure Stroke Unit  management is in place
  - Including dysphagia screening, DVT prophylaxis
- Management of acute complications
  - Hemicraniectomy for malignant oedema
- Stroke aetiology and early secondary prevention
- Appropriate rehabilitation
- Prevention and management of chronic complications

# Weigh benefits and risks for each individual patient

- Very strict exclusion criteria in initial trials
- tPA utilisation LOW (<5-10%)

- Very few absolute CI
  - Haemorrhage, BP not controllable, EIC too large, active or very high risk of bleeding

- Evidence that some were not CI
  - Eg. Age >80 years, >3h + DM

- Some are only considerations and not absolute
  - Eg. Mild or rapidly improving, Any stroke within 3 months

# Reducing DNT

- Helsinki model: Key components

1) ambulance prenotification with patient details alerting the stroke team to meet the patient on arrival

2) patients transferred directly from triage onto the CT table on the ambulance stretcher

3) tissue plasminogen activator (tPA) delivered in CT immediately after imaging

# First in Helsinki

Neurology. 2012 Jul 24;79(4):306-13. doi: 10.1212/WNL.0b013e31825d6011. Epub 2012 May 23.

## Reducing in-hospital delay to 20 minutes in stroke thrombolysis.

Meretoja A[1], Strbian D, Mustanoja S, Tatlisumak T, Lindsberg PJ, Kaste M.

Author information

**Abstract**

**OBJECTIVES:** Efficacy of thrombolytic therapy for ischemic stroke decreases with time elapsed from symptom onset. We analyzed the effect of interventions aimed to reduce treatment delays in our single-center observational series.

**METHODS:** All consecutive ischemic stroke patients treated with IV alteplase (tissue plasminogen activator [tPA]) were prospectively registered in the Helsinki Stroke Thrombolysis Registry. A series of interventions to reduce treatment delays were implemented over the years 1998 to 2011. In-hospital delays were analyzed as annual median door-to-needle time (DNT) in minutes, with interquartile range.

**RESULTS:** A total of 1,860 patients were treated between June 1995 and June 2011, which included 174 patients with basilar artery occlusion (BAO) treated mostly beyond 4.5 hours from symptom onset. In the non-BAO patients, the DNT was reduced annually, from median 105 minutes (65-120) in 1998, to 60 minutes (48-80) in 2003, further on to 20 minutes (14-32) in 2011. In 2011, we treated with tPA 31% of ischemic stroke patients admitted to our hospital. Of these, 94% were treated within 60 minutes from arrival. Performing angiography or perfusion imaging doubled the in-hospital delays. Patients with in-hospital stroke or arriving very soon from symptom onset had longer delays because there was no time to prepare for their arrival.

**CONCLUSIONS:** With multiple concurrent strategies it is possible to cut the median in-hospital delay to 20 minutes. The key is to do as little as possible after the patient has arrived at the emergency room and as much as possible before that, while the patient is being transported.

# Replicated in Melbourne

Neurology. 2013 Sep 17;81(12):1071-6. doi: 10.1212/WNL.0b013e3182a4a4d2. Epub 2013 Aug 14.

## Helsinki model cut stroke thrombolysis delays to 25 minutes in Melbourne in only 4 months.

Meretoja A[1], Weir L, Ugalde M, Yassi N, Yan B, Hand P, Truesdale M, Davis SM, Campbell BC.

⊕ Author information

**Abstract**

**OBJECTIVE:** To test the transferability of the Helsinki stroke thrombolysis model that achieved a median 20-minute door-to-needle time (DNT) to an Australian health care setting.

**METHODS:** The existing "code stroke" model at the Royal Melbourne Hospital was evaluated and restructured to include key components of the Helsinki model: 1) ambulance prenotification with patient details alerting the stroke team to meet the patient on arrival; 2) patients transferred directly from triage onto the CT table on the ambulance stretcher; and 3) tissue plasminogen activator (tPA) delivered in CT immediately after imaging. We analyzed our prospective, consecutive tPA registry for effects of these protocol changes on our DNT after implementation during business hours (8 am to 5 pm Monday-Friday) from May 2012.

**RESULTS:** There were 48 patients treated with tPA in the 8 months after the protocol change. Compared with 85 patients treated in 2011, the median (interquartile range) DNT was reduced from 61 (43-75) minutes to 46 (24-79) minutes ($p = 0.040$). All of the effect came from the change in the in-hours DNT, down from 43 (33-59) to 25 (19-48) minutes ($p = 0.009$), whereas the out-of-hours delays remain unchanged, from 67 (55-82) to 62 (44-95) minutes ($p = 0.835$).

**CONCLUSION:** We demonstrated rapid transferability of an optimized tPA protocol to a different health care setting. With the cooperation of ambulance, emergency, and stroke teams, we succeeded in the absence of a dedicated neurologic emergency department or electronic patient records, which are features of the Finnish system. The next challenge is providing the same service out-of-hours.

# How to improve?

- Look at best practices: eg Helsinki model
- AUDIT every case with everyone
  - Given tPA
  - Not given tPA
  - Including microtimes
- Small changes add up
- Monitor outcomes after changes

# Part 6: Challenges: Evidence-free areas in “standard” window

- Lots of emerging data on wider window, less emphasis on refining “standard” window

- But, still quite a lot about the early “standard” window we do not know about

# Example 1: What is the target BP in patients being treated with IV tPA?

- We know should be lower than 180 mmHg but how low to go?

- ENCHANTED PART B: AIS patients, thrombolysis-eligible patients, SBP>150 mmHg, within 6 h from onset
- intensive (target SBP 130-140 mm Hg within 1 h) or guideline (target SBP <180 mm Hg) for 72 h

- mRS distribution at 90 day: no difference
  - OR 1·01, 95% CI 0·87-1·17, p=0·8702)
- Lower rate of any intracranial haemorrhage in intensive group
  - 14.8% vs 18.7% p=0.0137

# Example 2: Small vessel stroke

- There are no RCT data specifically for sv stroke
- Non randomised data
  - 193 IV-TPA vs 2289 controls
  - Increased incidence of mRS 0-1 with IV-TPA treatment
    - adjusted OR 1.56 [1.06-2.29]; P = 0.0249
  - May be bias
- Risks
  - Infarct is small so ?lower haemorrhagic transformation
  - Associated leukoaraiosis → higher sICH esp remotely

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# Example 3: Low dose?

- Low dose used in some Asian countries

- ENCHANTED: did not prove non-inferiority

- Eligible for IV tPA within 4.5 h
- low-dose (0.6 mg/kg) vs standard dose (0.9 mg/kg)
- mRS 2-6 patients: low 53.2%, standard 51.1%, did not meet non-inferiority significance
- Low dose was non inferior for ordinal shift in mRS p=0.04
- Major sICH low 1.0%, standard 2.1%

# Challenges: In the era of ECR

- ECR data RATHER GOOD →Why bother with tPA?

- Reasons why tPA still relevant
  - Many do not have LVO and thus not eligible for ECR
  - Time to groin realistically > time to needle
  - Pre-tPA may assist recanalisation with ECR

- DIRECT SAFE trial recruiting…

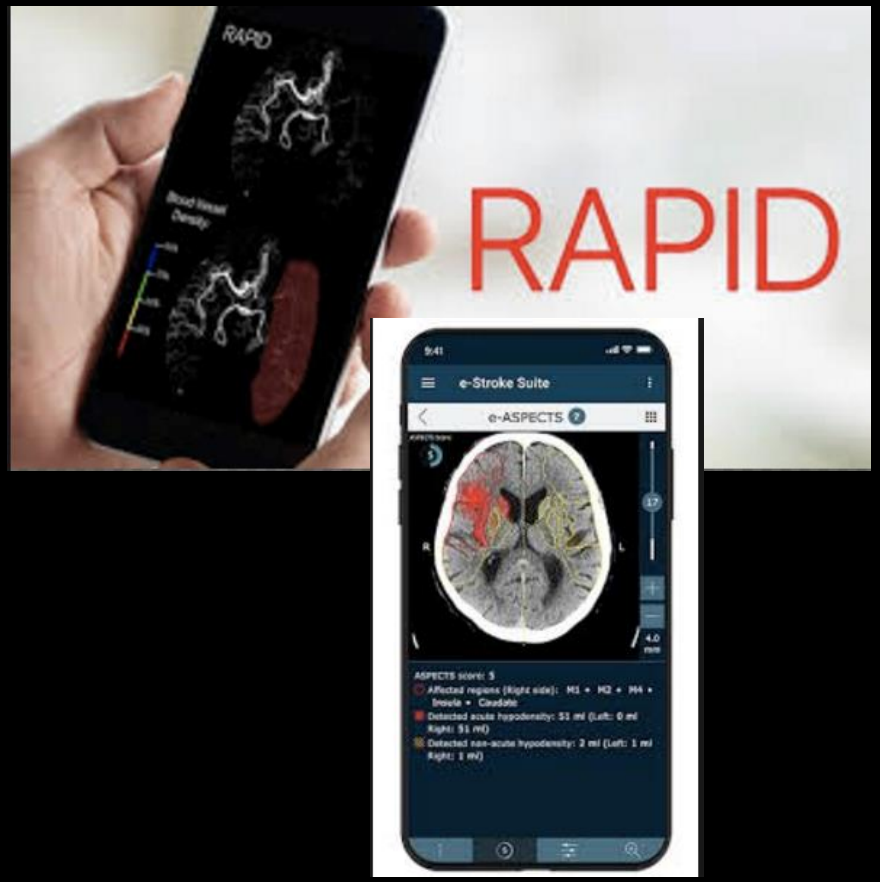
# Challenges: Distractions of new data

- Do not get too caught up in wider indications while missing opportunities for “standard” indications
  - Optimised work processes and improve efficiency
  - Consider where benefit may lie with limited resources
  - Public awareness as earlier reperfusion is always better
- Consider the screening yield
  - Use of manpower
  - Cost-effectiveness

# Part 7: Opportunities: in practice

- Mobile stroke units in the field


- Automated software for imaging assessment



# Opportunities: Targeted treatment

- Not one size fits all
- *Hypothetically*: Differentiate treatment for
  - a cardioembolic stroke causing a M2 obstruction
    - IV tenecteplase then ECR if persistent LVO
  - a M1 occlusion associated with ICLAD
    - Direct ECR with  stenting with no thrombolysis
  - Small vessel infarction with no LVO
    - IV alteplase low dose

# Opportunities: New horizons

- Re-emergence of neuroprotection?
- Physiological status, not by time clock?
  - Even if within 4.5h, should assess level of ischaemia
  - In very late window (>9h), there still may be salvageable tissue in some
- Better fibrinolytics?
  - Easier to administer, more fibrin specific, lower bleeding risk, lower allergic risk

# Thank you

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# Imaging considerations

- CT: aspects
- CTA: multiphasic, LVO
- CT perfusion

- MRI with MRA and perfusion
  - DWI FLAIR mismatch