# Thrombolysis for CVA

## When is it wise to lyse?

***Nepean WTET summary 2/6/20***

**Background and Rationale**

- Stroke continues to contribute towards significant morbidity and mortality
- Degree of reversibility and recovery often time critical. Therapies that can be delivered early are therefore desirable
- Initial premis was high quality evidence for thrombolysis in myocardial infarction – why not for CVA?
- More recent evidence supporting neurointervention describes a therapy still not accessible everywhere. Similarly compared usual care +/- ECR (endovascular clot retrieval) and so does not negate the need for knowing the ongoing indications for thrombolysis

**Advantages and Disadvantages**

- Advantages
  - Simple and cheap therapy, minimal skills required to administer
  - Offers an intervention to those geographically isolated from major stroke centers (CT brain, IV cannula, monitoring) in particular with evolving telemedicine to assist in specialist examination and decision making
- Disadvantages
  - Time critical; therapeutic window narrow
  - Not suitable to all; contraindications (e.g. therapeutic anticoagulation, uncontrolled hypertension, CVA or head injury <3/12, ) and no benefit in non-thrombotic CVA (calcium emboli, injectable material in IVDU with PFO)
  - Increase in intracranial haemorrhage (ICHg) and other major bleeding, increases early death (<7d)

**Evidence**

- **NINDS (US) 1995 NEJM**
  - Part 1; alteplase (tPA) versus placebo in two subgroups (0-90mins and 91-180mins) to see whether clinical improvement (improvement in NIHSS by 4 or more at 24h), n=291, no statistically significant difference between the groups
  - Part 2; sustained increase in patient with minimal/no deficit at 3m (assessors blinded from part one results) n=333, 12% absolute (32% relative) increase in patients with minimal or no disability (95-100 on Barthel index, BI), similar improvements in GOS, mRS, NIHSS
  - ICHg at 36h occurred in 6.4% of tPA group compared to 0.6% of placebo (n<0.001)
- **ECASS-1 1995 JAMA**
  - European large double blind RCT; acute ischaemic hemispheric stroke, moderate-severe neurological deficit, no major early infarct signs on CT randomised to tPA (alteplase 1.1mg/kg upto 100mg) versus placebo within 6h from onset of symptoms, n=620,
  - ITT analysis and target population (TP) analysis (expected 20% major protocol violations and indeed 17.4% occured eg randomised but not treated, concomitant heparin use etc)
  - No statistically significant difference in Barthel Index at 90d (+/-14d) in both ITT and TP
- **MAST-I (I=Italy) 1995 Lancet**
  - Aspirin (300mg daily for 10d) vs streptokinase (1.5MU over 1h) vs both vs neither; in acute stroke <6h
  - Streptokinase associated with increased early mortality (in particular when combined with aspirin) at 10d, at 6m streptokinase and/or aspirin arms marginally reduced severe disability
- **MAST-E (E=Europe) 1996 NEJM**
  - RCT streptokinase (1.5M) vs placebo within 6h of MCA stroke with moderate to severe ischaemia, n=310; primary outcome was RS =/>3 (severe disability) or death at 6m
  - Similar death and severe disability at 6m (79.5% vs 81.8%) with more deaths in treatment arm
  - Higher mortality at 10d in streptokinase group (34% vs 18.2% P=0.002) due to haemorrhagic transformation (symptomatic ICHg in hospital 21.25 vs 2.6%)
- **ASK (Australian StreptoKinase) 1996 JAMA**
  - DB RCT; 1.5MU streptokinase vs placebo for ischaemic stroke <3h and 3-4h, primary outcome reduction in morbidity (defined as BI <60) and mortality at 3m. N=340, stopped early for harm
  - Nonsignificant trend towards unfavourable outcomes with streptokinase arm (RR 1.08 95% CI 0.74-1.58) including increased mortality – poor outcomes confined to those >3h
  - Only a trend towards improvement in streptokinase arm in <3h group (RR unfavourable outcome 0.6 95% CI 0.28-1.58)

- **ECASS-2 1998 Lancet**
  - European-Australasian DB RCT acute ischaemic stroke without major infarct on CT stratified to 0-3h or 3-6h post symptom onset, randomised to 0.9mg/kg alteplase vs placebo. Primary endpoint mRS at 90d dichotomized favourable (0-1) vs unfavourable (2-6) outcome
  - Favourable outcome in 40.3% of alteplase vs 36.6% placebo groups (no statistical difference)
  - *Post-hoc analysis* of new dichotomised mRS of 0-2 as favourable outcome showed 54.3% vs 46% (p=0.024)
- **ATLANTIS B (JAMA 1999) and A (Stroke 2000)**
  - Part B: DB RCT alteplase versus placebo in acute ischaemic stroke between 3-5h post symptom onset n=613 (547 3-5h, 39 <3h, 24 >5h)
  - Excellent neurological outcome at 90d (NIHSS =/<1) – no difference (34% vs 32% p=0.65)
  - Increased mortality and ICHg at 90d
  - Part A: (initial study, halted early then recommenced as part B as above) 0-6h window; halted early for safety, n=142, increased ICHg (11% vs 0%) and mortality at 90d (23% vs 7%)
- **EPITHET 2008 Lancet neurol**
  - RCT alteplase vs placebo at 3-6h post stroke onset, with diffusion and perfusion imaging repeated at day 90 to see if tPA attenuates infarct growth (radiologically), n=101
  - Less infarct growth with tPA (p=0.001) and improved mRS 0-1 (36% vs 12%)
- **ECASS-3 2008 NEJM**
  - Following a pooled analysis of studies that suggested favourable outcome between 3-4.5h and that this was not associated with increased ICHg compared to <3h
  - DB parallel-group RCT initially 3-4h but early on extended to 4.5h; 1:1 0.9mg/kg (up to 90mg) alteplase vs placebo, n=821
  - More favourable outcome (mRS 0-1) with alteplase 52.4% vs 45.2% P=0.04, no significant increase in mortality, but more ICHg in alteaplse group 27% vs 17.6% P=0.001)
- **DIAS-2 2009 Lancet neurol**
  - DB RCT desmoteplase 90mcg/kg vs 125mcg/kg vs placebo at 3-9h with at risk tissue demonstrated on CT or MRI; n=193
  - Composite endpoint at 90d (improved NIHSS of =/>8, or NIHSS =/<1, mRS 0-2, BI 75-100)
  - No benefit with desmetoplase but less severe stroke (NIHSS and core size) in placebo group
- **IST-3 2012 Lancet**
  - International MC RCT (open label), rt-PA (0.9mg/kg up to 90mg) versus control for stroke up to 6h post symptom onset where no local indication or contraindication was met. Initial 276 patients double blinded, then open label
  - At 6m 37% (rt-PA) versus 35% (control) were alive and independent (as per the Oxford Handicap Score OHS 0-2) – non statistically significant. But a significant shift in OHS was seen
  - Elderly cohort (53% >80y/o) -no disadvantage in elderly, ICHg risk 7% vs 1%, as per other studies higher early mortality 11% vs 7% at 7d) but no difference by 6m with rt-PA
- **WAKE-UP 2018 NEJM**
  - MC RCT where unknown duration of stroke (and not planned for thrombectomy), ischaemia on DW-MRI but no hyperintensity on MRI FLAIR (suggesting likely <4.5h); alteplase vs placebo, n=503 (planned 800 but stopped early due to cessation of funding)
  - Primary outcome was mRS at 90d 0-1; 53.3% in treatment arm vs 41.8% in placebo P=0.02 (ICHg 2% vs 0.4%)
- **EXTEND 2019 NEJM**
  - MC RCT alteplase vs placebo 4.5-9h post stroke (or on awakening with stroke if within 9h from midpoint of sleep) in patients with hypoperfused but salvageable tissue on perfusion imaging, n=225 (of planned 310; terminated due to loss of equipoise from WAKE-UP trial)
  - Primary outcome mRS of 0-1 at 90d; 35.4% (alteplase) vs 29.5% P=0.04 (symptomatic ICHg 6.2% vs 0.9% P=0,05)

**Summary (my practice)**

- Controversial – many negative studies, total number of patients across all studies is low, positive studies difficult to pool due to diverse choice of end points and stroke severity scores. Not endorsed by all societies (but is by ASA/AHA)
- Do not use Streptokinase. Thrombolytic of choice is alteplase (at dose of 0.9mg/kg up to 90mg with 10% given as a bolus over one minute, remainder over 60mins), no aspirin for at least first 24h after thrombolysis (usually give 24-48h)
- Positive studies seemed to show no initial benefit in neurological outcome at 24h, but more favourable outcomes at 3m
- Thrombolyse if clinical picture in keeping with stroke, where available perfusion imaging suggestive of ischaemia and no contraindications -thrombolyse 0-3h, extended criteria up to 4.5h as per ECASS-3 (best evidence in <80y/o no DM/CVA no oral anticoagulants and CVA not involving >1/3 MCA territory on imaging) +/- beyond this in select patients as per ASA/AHA with stroke specialist input and discussion with patient/family of risks
- Open and honest discussions; improves functional outcome, but increases early death (<7d) and symptomatic ICHg up to 10x
- In centers with no close access to perfusion imaging; non haemorrhage on CT, clinical picture in keeping with CVA, euglycaemic state, in absence of contraindications is all that is required according to ASA/AHA guidelines (do not delay)
- Refer for ECR if appropriate without delay (do not wait to assess success of thrombolysis)