# Thrombolytic therapy should be first line treatment in ischemic stroke

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# Stroke as an Emergency

- Background
  - Stroke is the most important cause of morbidity and long term disability in world
  - Demographic changes are likely to result in an increase in both incidence and prevalence
  - Stroke is also the second most common cause of dementia, the most frequent cause of epilepsy in the elderly, and a frequent cause of depression[2,3]

1: Rothwell PM et al. Lancet (2005) 366:1773-1783
2: O'Brien JT et al. Lancet Neurol (2003) 2:89-98

# Emergency Management

- The time window for treatment of patients with acute stroke is narrow
  - So Time is the most important factor

# Thrombolytic Therapy (i.v. rtPA)

- Background (NINDS[1], ECASS I[2] + II[3], ATLANTIS[4])
  - Intravenous rtPA (0.9mg/kg, max 90mg) given within 3 hours of stroke onset, significantly improves outcome in patients with acute ischaemic stroke
  - Benefit from the use of i.v. rtPA beyond 3 hours is smaller, but may be present up to at least 4.5 hours

1: NINDS rt-PA Grp: New Engl J Med (1995) 333:1581-1587
2: Hacke W et al.: JAMA (1995) 274:1017-1025
3: Hacke W et al.: Lancet (1998) 352:1245-1251
4: Clark WM et al.: Jama (1999) 282:2019-26.

- Symptomatic intracerebral hemorrhage (SICH) risk is the factor most likely to preclude tissue plasminogen activator (tPA) use by emergency physicians.

tPA for stroke—potential benefit, risk, and alternatives; education tool. Available at: http://aaem.org/education/tpaedtool-AAEM.pdf. Accessed May 22, 2007.

- suggests that 8 of 18 stroke patients who receive tPA will have a good recovery by 3 months after the event.
- 6 of 18 stroke patients who recover substantially with good outcome without tPA.
- bleeding into the brain, with high probability of death, will occur in 1 of 18 patients receiving tPA.
- No patients are visualized to experience an intracerebral bleed or die without tPA.

# What is the balance of RISK and BENEFIT?

- Recanalization rates with in 24 hrs after the thrombolytic therapy (t-PA) are low
    - 14% in internal carotid arteries
    - 55% in middle cerebral arteries 1

1: Rha JH. Saver JL. The impact of recanalization on ischaemic stroke outcome: a metaanalysis. Stroke 2007;38:967-73

# Contd.

- Use of such a tool in clinical practice would be problematic, misleading, and would erroneously convey an unfavorable benefit–risk ratio.

# NINDS inclusion and exclusion criteria for tPA therapy for acute ischemic stroke

**Inclusion criteria (patient must have all three of the following)**

- Ischemic stroke within 180 minutes of onset, with a clearly defined time of onset or when the patient was last known to be intact
- Neurologic deficit measurable on the NIH Stroke Scale, and appropriate for such therapy
- CT scan of the brain showing no evidence of intracerebral hemorrhage or signs of significant early infarct

# Exclusion criteria (patient must have none of the following)

- Stroke or serious head trauma within the preceding 3 months
- Major surgery within 14 days
- History of intracerebral hemorrhage
- Systolic blood pressure above 185 mm Hg, diastolic blood pressure above 110 mm Hg,
- or aggressive treatment required to reduce blood pressure to these limits
- Rapidly improving or minor neurologic symptoms
- Symptoms suggestive of subarachnoid hemorrhage
- Gastrointestinal hemorrhage or urinary tract hemorrhage within the previous 21 days
- Arterial puncture within the previous 7 days at a noncompressible site
- Seizure at the onset of the stroke
- Current use of oral anticoagulants
- Prothrombin time greater than 15 seconds
- Heparin within 48 hours preceding the onset of the stroke with an elevated partial thromboplastin time
- Platelet count < 100,000/mm3
- Glucose concentration < 50 mg/dL or > 400 mg/dL

## Cautionary signs (not contraindications, but should alert the physician's concern)

- Severe neurologic deficit, with an NIH Stroke Scale score > 22, especially in an elderly patient
- Early signs of acute stroke on CT scan: evidence of large middle cerebral artery involvement with hypodensity,
- blurring of the gray-white margins, or sulcal effacement in > 1/3 of the middle cerebral distribution

ADAPTED FROM NINDS AND STROKE rt-PA STROKE STUDY GROUP. TISSUE PLASMINOGEN ACTIVATOR FOR ACUTE ISCHEMIC STROKE. N ENGL J MED 1995; 333:1581–1587.

| Trial | Drug | Dose | Interval (hours) | Symptomatic ICH | | Primary Outcome |
|---|---|---|---|---|---|---|
| | | | | *Treated* | *Control* | |
| MAST-I, 1995 (5) | Streptokinase | 1.5 μU | 0-6 | 16% | 2.6% | No difference between groups |
| MAST-E, 1996 (6) | Streptokinase | 1.5 μU | 0-6 | 21.2% | 4.6% | No difference between groups |
| ASK, 1996 (7) | Streptokinase | 1.5 μU | 0-4 | 12.6% | 2.4% | No difference between groups |
| ECASS, 1995 (8) | t-PA | 1.1 mg/kg | 0-6 | 19.8% | 6.5% | No difference between groups in BI and mRS scores at 90 days |
| NINDS, 1995 (9) | t-PA | 0.9 mg/kg | 0-3 | 6.4% | 0.6% | No difference between groups at 24 hours; significant improvement in functional status at 90 days in treated group (global odds ratio for favorable outcome, 1.7 [95% CI, 1.2-2.6]) |
| ECASS II, 1998 (10) | t-PA | 0.9 mg/kg | 0-6 | 8.8% | 3.4% | No difference between groups |
| ATLANTIS, 1999 (11) | t-PA | 0.9 mg/kg | 3-5 | 7.0% | 1.1% | No difference between groups |

# First Do No Harm

Thrombolytic
therapy does significantly increase the risk of intracranial
hemorrhage in patients with stroke.

Its major shortcoming for routine application is the

- Short therapeutic window of 3 hours.
- should be restricted to neurologists or other disciplines with expertise in neurological emergency and CT reading.

- Intravenous recombinant t-PA is indeed not a magic bullet.
- Some patients will fare better with t-PA, some will have no benefit, and unfortunately some will fare worse.
- In an ideal world, we would be able to individualize our treatment options for patients with stroke rapidly, using both expert clinical acumen and appropriate ancillary studies.

# Cochrane systematic review of the evidence for thrombolytic therapy in acute ischaemic stroke

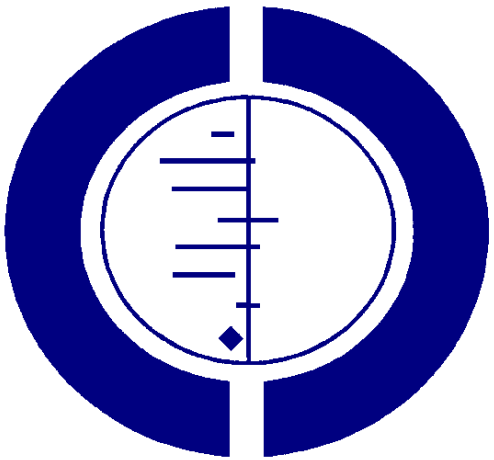
Joanna Wardlaw

abstract available free at:

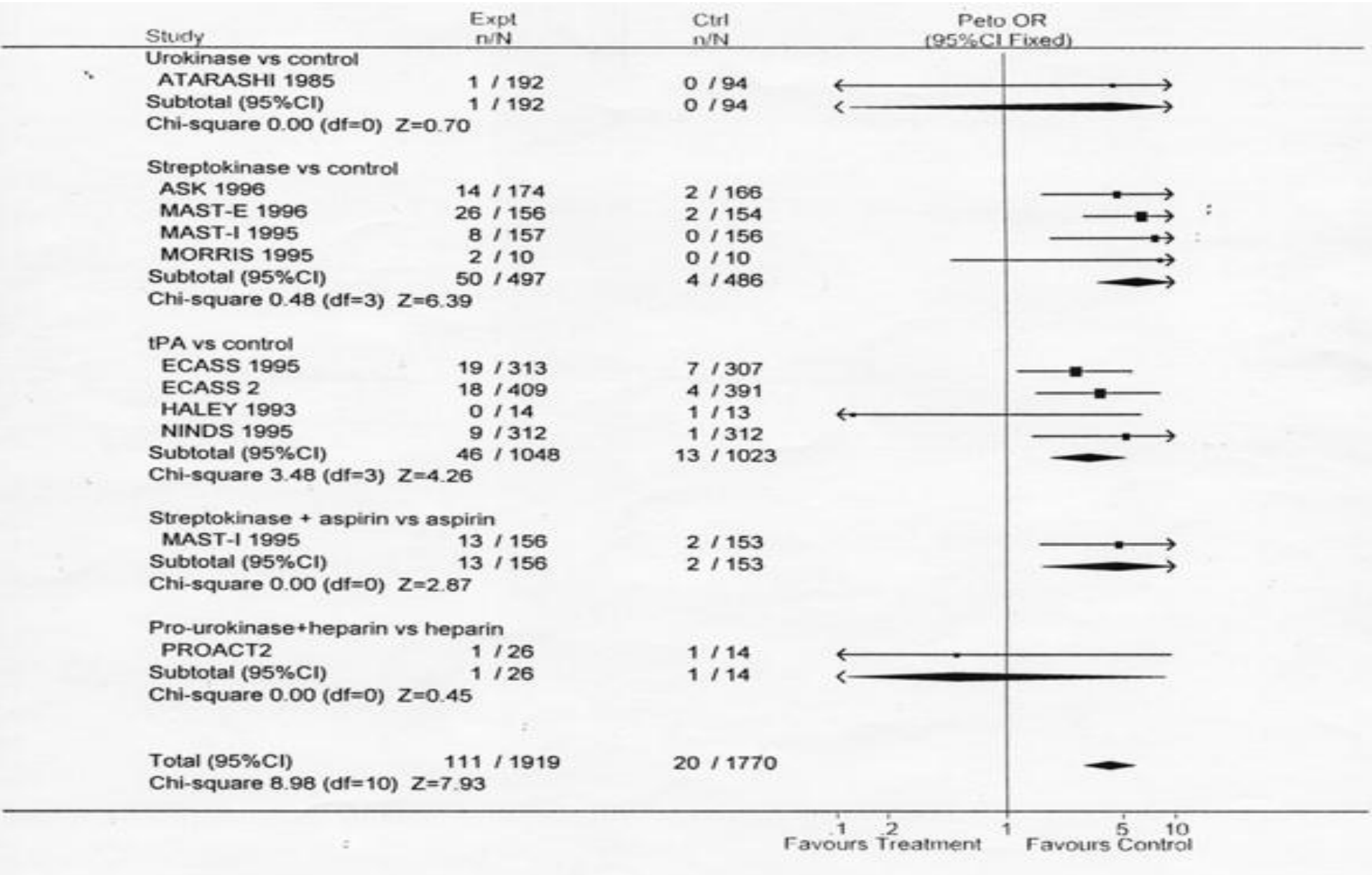
**www.dcn.ed.ac.uk/csrg**

or on CDROM

**The Cochrane Library**



# Fatal intracerebral haemorrhage (ICH) with thrombolysis for ischaemic stroke



# ICH after thrombolysis for ischaemic stroke

- Fatal ICH increased from 1% to 5%.
  - five fold increase ($p<0.00001$)
  - **50** extra fatal ICH per 1000 treated
- Fatal or non-fatal symptomatic ICH increased from 3% to 10%.
  - three fold increase ($p<0.00001$)
  - **70** extra haemorrhages per 1000 treated
- Similar proportional increase in ICH with different thrombolytic agents

# Indications for early aspirin use in acute ischaemic stroke: a combined analysis of over 40,000 randomised patients from CAST and IST

Sandercock PAG, Chen ZM, on behalf of IST and CAST collaborative groups

Stroke 2000; 31:1240-49.

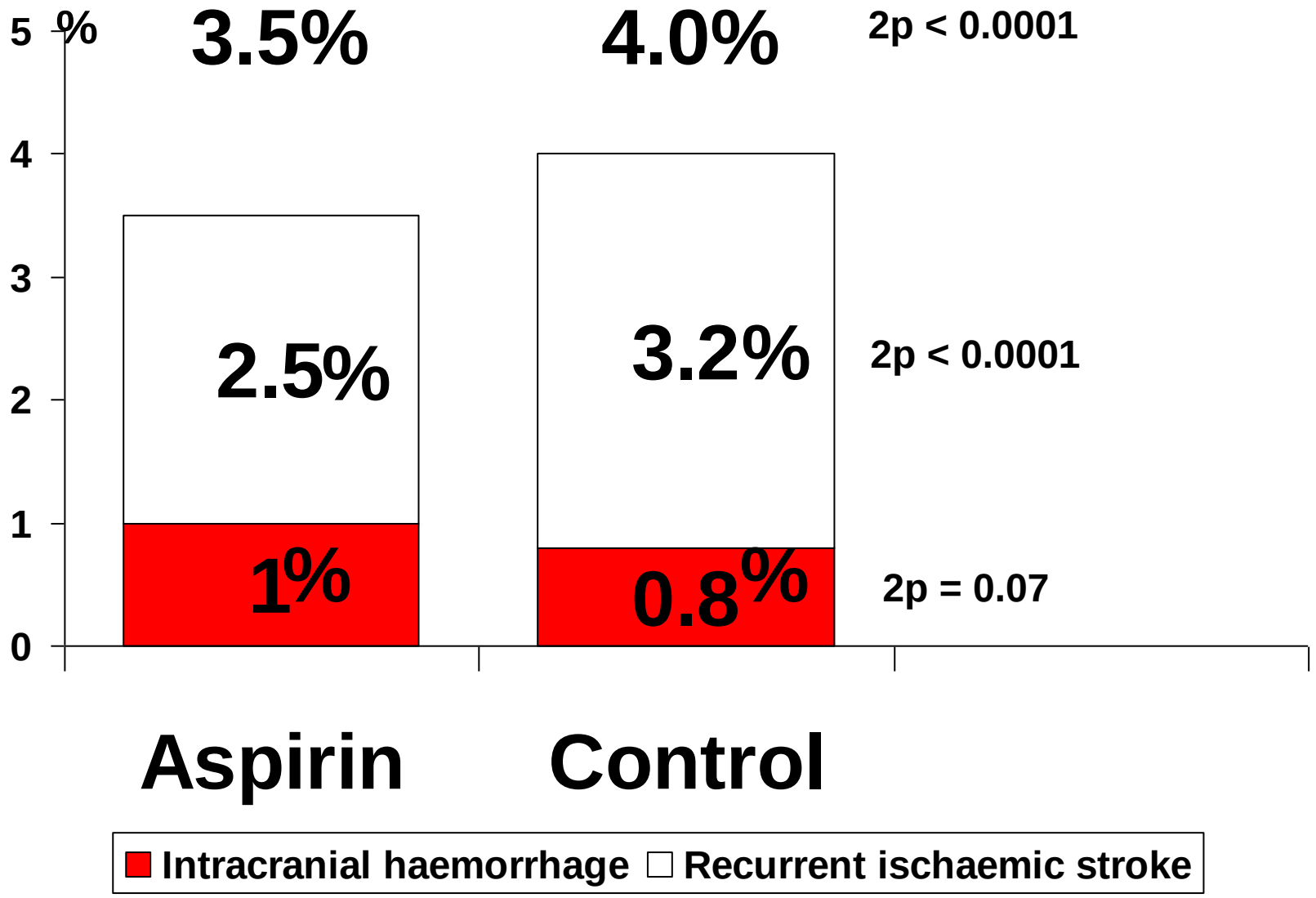
# Design features of CAST & IST

- Randomised
- Acute ischaemic stroke <48 hours
- CT **before** entry where possible, or soon after
- Aspirin dose (scheduled treatment period):
  - IST: 300mg daily vs open control (2 weeks)
  - CAST: 160mg daily vs placebo control (4 weeks)

# Patients included in the trials

| | CAST | IST |
|---|---|---|
| **No. randomised** | 20,655 | 19,435 |
| **CT scan** | | |
| - Before entry | 87% | 68% |
| - Total | 97% | 96% |
| **Heparin allocation** | 0 | 50% |

# Recurrent ischaemic stroke or intracranial haemorrhage during treatment period



# Summary of aspirin benefit

- For every 1000 patients started < 48 hrs of onset:
  - **< 14 days**, 7 avoid recurrent ischaemic stroke
  - **at 6 months**, 12 avoid death or dependency, & an extra 10 make a complete recovery
- The risk of cerebral haemorrhage is low (1-2 per 1000) and is completely outweighed by the benefits
- Early aspirin is of net benefit for a wide range of patients, so prompt treatment should be considered for almost all patients presenting with suspected acute ischaemic stroke.

# What have we learned about thrombolysis, anticoagulants and aspirin?

- Thrombolysis: promising, but applicable to 1% of all ischaemic strokes? Need much larger-scale trials.
- Anticoagulants/heparin: benefits balanced by bleeding risk. No net benefit.
- Aspirin. Modest benefits, but applicable to almost all patients. Like thrombolysis for AMI
- Effort and audit needed to ensure **ALL** patients with acute ischaemic stroke get aspirin
  - CT has excluded haemorrhage?
  - patient able to swallow safely? -> oral aspirin
  - not able to swallow? -> rectally or via NG tube

# Thank You all