THROMBOLYSIS

In Acute Ischaemic Stroke
‘Time is brain’
and..
‘Competence is Brain’
Definition of a stroke

• “A focal (or at times global) neurological impairment of sudden onset and lasting more than 24 hours (or leading to death) and of presumed vascular origin.”

• “A stroke is a neurological impairment caused by a disruption in blood supply to a region of the brain lasting more than 24 hours”

WHO 2005 / ASA 2006
23% of stroke patients gave a history of a preceding TIA

TIA or Stroke

In both TIA and stroke, brain vessel is occluded and ischaemia occurs.
What it is all about..

Ischaemic  85%

Haemorrhagic  15%
Consider that..

- Every 5 minutes someone in the UK has a stroke.

- Stroke is the 3rd biggest killer and a leading cause of severe adult disability in the UK.

- Almost 1:4 men and 1:5 women aged 45 can expect to have a stroke if they live to 85.

- More than 3 times as many women die from stroke than breast cancer in the UK.

- For every £50 spent on cancer research and £20 on heart disease research, only £1 is spent on stroke research.

Stroke Association 2008
The National Audit Office report 2005
Department of Health
Reducing Brain Damage: Faster access to better stroke care
Nov 2005
Costs to the economy

- There are at least 300,000 people in England living with moderate to severe disabilities as a result of stroke.

- Stroke care costs the NHS about £2.8 billion a year in direct care costs
  - more than the cost of treating coronary heart disease
  - and £1.8 billion in lost productivity and disability.

- Additionally, the annual informal care costs are around £2.4 billion.

- Total costs £5-7 billion
Costs to the economy

- In leading hospitals in Australia around 9% of patients are thrombolysed and about 40% of these patients then fully recover from their strokes.

- Rates of thrombolysis in England are <1%.

- Achieving thrombolysis in 9% of patients with AIS could generate net savings to the NHS of over £16 million a year, with more than 1,500 patients fully recovering from their strokes each year who would not otherwise have done so.
Stroke Development & Time

6 Hours into Stroke

Infarct

Penumbra
Stroke Development & Time

24 Hours into Stroke

Infarct
Penumbra
Stroke Strategy

- **Rapid specialist care concentrated in centres of excellence.**

- **10% of patients having access to thrombolysis treatment.**

- **Hub and spoke model of care - provision of hyperacute stroke care at a specialist unit before decanting for rehabilitation closer to home.**

(DOH) Mending Hearts & Brains 2006
Stroke Strategy

- Ambulance trusts should manage patients with a suspected stroke as a Category A call - FAST and PRE-ALERT

- All patients with suspected stroke should be transferred immediately to a hospital providing acute stroke services

  - Stroke triage system
  - Provision of expert clinical assessment
  - Timely imaging
  - Delivery of thrombolysis (24hrs)
  - 24hr availability of brain scanning
  - Opinion of a Consultant stroke specialist available as required

(DOH) Mending Hearts & Brains 2006
Stroke Strategy

- Patients with suspected stroke should receive an immediate structured clinical assessment in A&E

- All patients with suspected stroke should be scanned as rapidly as possible (Next available slot/60 mins - out of hours)

- All stroke patients should have access to high quality stroke specialist care

- Specialist neurointensivist care should be rapidly available through collaboration and commissioning where needed.

(DOH) Mending Hearts & Brains 2006
Questions
Cerebral Circulation and patho-physiology
Risk Factors for AIS

Modifiable
- Transient ischaemic attack
- Hypertension
- Cardiac function (AF)
- Dyslipoproteinaemia
- Smoking
- Diabetes
- Alcohol
- Cocaine

Non-Modifiable
- Age
- Gender
- Ethnicity
- Familial history

Goldstien et al. 2001
Brain tissue cannot survive without O² and glucose. Although only 2% of total body weight the brain accounts for 25% of O² consumption.

Within 10 seconds of ischaemia there is loss of consciousness, 20 seconds electrical activity ceases, after a few minutes irreversible brain damage begins (Brain damage also occurs when brain goes without glucose for 10-15 minutes).
Background

- Normal blood flow is 55ml/100g/min of brain tissue.

- Reduction to about 20ml/100g/min causes neurons to stop generating electrical signals.

- Reduction to about 10ml/100g/min results in infarction and lead to a stroke.
Cerebral Blood Supply

The arterial blood supply to the brain is derived from two pairs of vessels:

- **Anterior** - Internal Carotid Arteries (80%)
- **Posterior** - Vertebral Arteries (20%)
Cerebral Blood Supply

Internal carotid artery gives rise to:

- Anterior cerebral arteries (ACA)
- Middle cerebral arteries (MCA)
- Anterior choroidal artery (AchA)
- Posterior communicating artery (PCA)
Cerebral Blood Supply

- **Anterior cerebral arteries** supply blood to:
  - medial surfaces of the frontal and parietal lobes, cingulate gyrus, basal ganglia, and corpus callosum.

- **Middle cerebral arteries** supply blood to:
  - lateral surfaces of the frontal, occipital, temporal and parietal lobes and lenticulostriate arteries
Cerebral Blood Supply

Vertebral arteries gives rise to:

- Basilar cerebral artery (BCA)
- Posterior cerebral arteries (PCA)
- Anterior inferior communicating artery (AICA)
Cerebral Blood Supply

- Basilar cerebral artery
  supply blood to:
  - Internal ears, pons & cerebellum

- Also gives rise to the Posterior cerebral arteries.
  Supply blood to:
  - Midbrain, occipital lobe & medial surfaces of the temporal lobe
Cerebral Veins

- Cerebral veins are divided into Superficial and Deep groups.

- They eventually empty into the internal jugular veins and then to the right atrium of the heart.
Questions
Aetiology of Stroke

- **Cardioembolic**
  - AF, mural thrombus, patent foramen ovale, infective endocarditis
  - AF, which is found in less than 5% of the general public, is found in around 25% of patients admitted with stroke.
Aetiology of Stroke

• Atherothromboembolic

- Carotid / vertebral atheroma, cerebral artery occlusion, carotid dissection

- The development of atheroma within the carotid and vertebral arteries is the same as in any other artery. Patients presenting with stroke due to arterial disease are likely to have evidence of ischaemic heart disease and/or peripheral vascular disease.
Aetiology of Stroke

- Small Vessel Disease

  - Hypertensive arterial disease, diabetic vasculopathy, vasculitis

  - Small vessel disease resulting from occlusion of small arteries in the brain, is most frequently associated with hypertension, diabetes and dyslipoproteinaemia. Occasionally, it can result from micro-emboli in the heart or carotid arteries
Aetiology of Stroke

- Haemorrhagic
  
  - Hypertensive arterial disease, Amyloid angiopathy, Arteriovenous malformation, Aneurysm
  
  - In ICH, pressure from the space-occupying blood clot causes damage to brain tissue. Rupture from a large vessel will often be rapidly fatal. Hypertension is the main underlying cause of ICH. SAH most commonly arises from a congenital aneurysm of a major vessel. It is one of the more common reasons for stroke in younger adults.
Atherosclerosis
Questions
Diagnosis of Acute Ischaemic Stroke
Diagnosis of Acute Ischaemic Stroke

Introduction

- Stroke should be considered a “brain attack” with emphasis placed upon rapid diagnosis, evaluation and treatment. Remember “Time is brain”
- Early recognition by patient or bystander is essential
- Emergency medical services must be called immediately
- Emergency medical services must perceive stroke as a similar emergency to AMI and trauma
Diagnosis of Acute Ischaemic Stroke

Goals of diagnosis

- Determine that neurological symptoms are due to stroke and exclude non-vascular reasons for symptom
- Determine the type of stroke e.g. haemorrhagic or ischaemic
- Determine the location of brain injury to assess the size of the stroke
- Determine the most likely cause of the vascular lesion
- Detect any acute neurological or medical complications
Diagnosis of Acute Ischaemic Stroke

Differential diagnosis of acute stroke

- Ischaemic stroke
- Haemorrhagic stroke
- Craniocerebral trauma
- Brain abscess
- Encephalitis
- Brain tumours
- Seizure
- Hypoglycaemia
- Migraine headache
## Diagnosis of Acute Ischaemic Stroke

### Differential diagnosis of acute stroke

<table>
<thead>
<tr>
<th>FEATURES SUGGESTING HAEMORRHAGIC STROKE</th>
<th>FEATURES SUGGESTING ISCHAEMIC STROKE</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Early and prolonged loss of consciousness</td>
<td></td>
</tr>
<tr>
<td>• Prominent headache, nausea and vomiting</td>
<td></td>
</tr>
<tr>
<td>• Retinal haemorrhages</td>
<td></td>
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<tr>
<td>• Nuchal rigidity</td>
<td></td>
</tr>
<tr>
<td>• Focal signs do not fit the anatomic pattern of a single blood vessel</td>
<td></td>
</tr>
<tr>
<td>• Stepwise deterioration or progressive worsening</td>
<td></td>
</tr>
<tr>
<td>• Waxing and waning of findings</td>
<td></td>
</tr>
<tr>
<td>• Focal neurologic impairments in the pattern of a single blood vessel</td>
<td></td>
</tr>
<tr>
<td>• Signs point to a focal cortical or sub cortical lesion</td>
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</tbody>
</table>
### Diagnosis of Acute Ischaemic Stroke

**Clinical features of stroke**

| TIME COURSE AND EVOLUTION | • Sudden or rapid onset  
| • Reach maximal intensity within 24 hrs |
| FOCAL NEUROLOGICAL SYMPTOMS | • Headache  
| • Nausea and vomiting  
| • Altered mental status (syncope, seizure, coma)  
| • Hypertension and abnormal vital signs  
| • Nuchal rigidity |
| GLOBAL SYMPTOMS AND SIGNS | • Cognitive impairments (i.e. Aphasia, neglect, etc.)  
| • Weakness or incoordination of limbs  
| • Facial weakness  
| • Numbness of limbs and/or face |
Diagnosis of Acute Ischaemic Stroke

Diagnostic tools

• Variety of diagnostic tools available, and should be performed urgently

• Medical history may reveal risk factors, stroke type and area of brain affected

• Physical examination will help uncover underlying pathology

• CVS assessment might provide evidence of cause or detect cardiovascular complications

• Computed tomography is most reliable way to differentiate haemorrhagic stroke from ischaemic stroke
Diagnosis of Acute Ischaemic Stroke

CT scanning

- Most important initial diagnostic study
- Current gold standard for ruling out haemorrhagic stroke. It is:
  Widely available, non-invasive, quick, relatively inexpensive, relatively easy to interpret

- But limitations because:

  Ability to detect cerebral infarction depends upon size, location and age of lesion. Infarcts smaller than 5 mm may escape detection, only around 5% are visible within the first 12 hours of stroke onset
Diagnosis of Acute Ischaemic Stroke

MRI scanning

- MRI has some advantages over CT scanning:
  
  *It is more sensitive to changes in tissue structure*
  *It provides a more accurate and earlier measure of cerebral infarction*

- However, it also has some limitations:
  
  *It is more expensive than CT*
  *It is less widely available*
  *It requires special expertise*
## Mortality and Disability

<table>
<thead>
<tr>
<th></th>
<th>TACI</th>
<th>PACI</th>
<th>LACI</th>
<th>POCI</th>
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<td><strong>Death</strong></td>
<td>39</td>
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<td>2</td>
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<tr>
<td><strong>Dependant</strong></td>
<td>56</td>
<td>39</td>
<td>36</td>
<td>31</td>
</tr>
<tr>
<td><strong>Independent</strong></td>
<td>4</td>
<td>56</td>
<td>62</td>
<td>62</td>
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</table>

Bamford et al Lancet 1991
Questions
Elements of patient Pathway

- Pre-hospital
- Emergency Department
- Radiology
- Acute Stroke Unit
Pre-Hospital Stroke Care
Paramedic Responsibilities

• Ambulance response - Cat A
• Patient assessment - FAST
• Blood glucose - hypo/hyperglycaemia
• Appropriate hospital pre-alert - saying “FAST positive stroke patient” - A&E / stroke team (dedicated bleep?)
• Correct positioning of stroke patient - conscious (semi-sitting)
  unconscious (stable side position, paralysed limb uppermost)
• Patient relative (if possible) - time of onset / consent
Potential eligibility for thrombolysis

- FAST positive
- Onset within last 2 hours
- Aged 18 - 80
- Conscious or easily rousable
- No seizures / fits
- BM > 3mmols
- Not on Warfarin
Does FAST work?

<table>
<thead>
<tr>
<th>Element</th>
<th>Paramedic</th>
<th>Neurologist</th>
</tr>
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<tbody>
<tr>
<td>Face</td>
<td>F</td>
<td>68</td>
</tr>
<tr>
<td>Arm</td>
<td>A</td>
<td>96</td>
</tr>
<tr>
<td>Speech</td>
<td>S</td>
<td>79</td>
</tr>
<tr>
<td>Test</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

% recorded signs in 217 patients with confirmed stroke \(^1\)

Paramedics correct in 144/183 (79%) using FAST Test \(^2\)

FAST

Face - Ask the patient to smile or show teeth and look for NEW lack of symmetry

Arm - Ask the patient to lift their arms together and hold for 5 seconds. Does one arm drift or fall down. The arm with motor weakness will drift downwards compared to the unaffected limb

Speech - Ask the patient to repeat a phrase. Assess for slurring or difficulty with the words or sentence
Emergency Department
Emergency Department

Assessment

- Confirm time of onset
- Exclude hypoglycaemia
- Define neurological deficit (ROSIER)
- IV access - bloods (FBC, clotting, glucose, U&E, PT, aPTT, INR, cardiac enzymes + ECG)
- NIHSS
- Medications (warfarin)
- Assess patient weight
- Request Urgent CT scan
- Complete thrombolysis checklist
- Inform patient / relative potential candidate for thrombolysis
## ROSIER

**Date/time of symptom onset**

<p>| | | | | | | |</p>
<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
</table>

**GCS**

- **E=** [ ]
- **V=** [ ]
- **M=** [ ]

**BP** [ ]

**BM** [ ]

(if BM <3.5mmols treat urgently and reassess once blood glucose normal)

Has there been loss of consciousness or syncope

- **Y(1)** [ ]
- **N(0)** [ ]

Has there been seizure activity

- **Y(1)** [ ]
- **N(0)** [ ]

Is there a NEW ACUTE onset or on awakening from sleep

<table>
<thead>
<tr>
<th>Symptom</th>
<th><strong>Y(1)</strong></th>
<th><strong>N(0)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymmetric facial weakness</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>Asymmetric arm weakness</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>Asymmetric leg weakness</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>Speech disturbance</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>Visual field deficit</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

**Total score** [ ] (-2 to +5)
NIHSS

- The NIHSS assesses neurological impairment such as:
  - Paresis
  - Aphasia
  - Level of consciousness
  - Sensory symptoms
  - Facial and gaze palsy
  - Dysarthria and hemi-neglect

- It shows good inter-rater reliability and validity, which can be increased by video-assisted training and self assessment
- It has a score range from 0 to 42; death is not coded

NIHSS is the most commonly used assessment tool for stroke thrombolysis.
Emergency Department

Stroke Mimics

Neurological
- Seizure/postictal state
- Complicated migraine
- Subdural Haematoma
- Abcess, tumour or malignancy
- Hypertensive encephalopathy
- Multiple sclerosis (or other demyelinating process)
- Vertigo
- Cranial and peripheral neuropathies
Emergency Department

Stroke Mimics

Neurological (cont)
- Spinal cord or disc disease
- Transient global ischaemia
- Bell’s Palsy
- Encephalitis

Metabolic
- Hypo/hyperglycaemia
- Hyponatraemia
- Hepatic encephalopathy
Emergency Department

Stroke Mimics

Metabolic (cont)
  • Drug overdose

Other
  • Syncope
Emergency Department

What the clinician needs to know

- Has a stroke occurred or are the patient’s symptoms due to a different pathology?
- If a stroke has occurred, is it a haemorrhagic stroke or a cerebral infarction?
- Is there a treatable underlying aetiology for the patient’s acute stroke?
- Is the territory of the ischaemic insult salvageable or are the tissues already irreversibly infarcted?
Imaging Interpretation
What to look for in the first CT scan

There are a number of features that should be looked for in the initial CT scan. These are:

- A spot or tubular structure along the major intracranial vessels particularly at the intracranial bifurcation of the internal carotid artery, along the basilar artery or along the middle cerebral artery, which is hyperdense in relation to the remainder of the vessel or to other vessels. This indicates the presence of a clot within the vessel.
Image Interpretation

What to look for in the first CT scan

- Early parenchymal hypodensity of the basal ganglia and/or the cortex, possibly associated with sulcal effacement or ventricular compression, indicating the extent of the affected tissue.

- Parenchymal hyperdensity which may represent parenchymal haemorrhage. Haemorrhages may be difficult to see at this early stage and may appear as a tiny white spot.

- Evidence of previous ischaemic brain damage, the pattern of which may indicate the underlying disease.
Estimating extent of early ischaemic damage

If a patient is being assessed for thrombolysis, there may not be time for quantitative measurement of parenchymal hypodensity.

The investigators of the ECASS trial concluded that patients with hypodensity comprising more than 33% of the MCA territory should not be considered for thrombolysis.
Hyperdense cerebral vessels

A useful early sign of cerebral Ischaemia is the appearance on The CT of hyperdense vessels

As clotted blood possesses a higher absorption value on CT than moving blood, any intraluminal clotted blood makes the affected artery stand out against lower density unaffected arteries
Hyperdense middle cerebral artery sign
(HMCAS)

The MCA is the commonest vessel to be occluded in cerebral Ischaemia and is considered a reliable early sign of impending infarction.

Occasionally, however, a patient with HMCAS may show no infarction because of good collateral flow.
Hyperdense posterior cerebral artery (HPCAS) and hyperdense internal carotid artery sign (HICAS)

The HPCAS and HICAS are found much less commonly than the HMCAS

Often the disappearance of the hyperdense sign indicates that recanalisation therapy has been successful
Parenchymal hypodensity as a predictor of neurological outcome

The hypodensity that develops during the first hours after the onset of cerebral ischaemia may be predictive of eventual outcome but it is often very subtle and difficult to define.
Consequences of hypodensity for therapy

Parenchymal hypodensity as shown on CT within 6 hours of stroke onset represents the early stages of necrosis in the core of an ischaemic infarct.

Following stroke, the lentiform nucleus frequently appears hypodense on CT due to its poor collateral supply.
Ischaemic brain oedema and CT

Parenchymal hypodensity during the first six hours after stroke is often accompanied by brain swelling.

There is often effacement of cortical sulci with loss of grey-white matter differentiation, which can best be detected by comparing the two hemispheres.

"Early CT Diagnosis of Acute Ischaemic Stroke: A Physicians’ Guide" produced by MediCine International plc for Boehringer Ingelheim GmbH
CT or MRI?

Non-contrast CT

- Recommended initial neuro-imaging
- CT not ideal, because of difficulty in detecting acute or small infarcts and artifact in the brainstem area
- CT can identify subtle signs of early ischaemia or arterial occlusion

MRI

- Better for detection of acute ischaemia than CT - sensitivity and specificity of diffusion-weighted imaging for detecting acute ischaemia are about 100%
- Diffusion-weighted imaging also provides the additional advantage of visualisation of small lesions, usually poorly visualised on CT

Newer CT methods:

- CT angiography, CT perfusion, and CT cerebral-blood volume imaging can obtain similar information to MRI.

Questions
Thrombolysis

Alteplase (rtPA) approved for use in ischaemic stroke 2002 in Europe

- Randomised trials:
  - NINDS 624pts randomised <3hrs
  - ECASS I 620pts randomised <6hrs
  - ECASS II 800pts randomised <6hrs

- 1 registry
  - SITS MOST 4961 pts <3 hrs

NINDS: National Institute of Neurological Disorders and Stroke
ECASS: European Cooperative Acute Stroke Study (as required by EMEA in support of European licence)
SITS-MOST: Safe Implementation of Thrombolysis in Stroke Monitoring Study
**Thrombolysis trials**

National Institute of Neurological Disorders and Stroke Study (NINDS), 1995

624 patients; onset <3 hours, randomised to rt-PA (0.9mg/kg) or placebo

“Compared with patients given placebo, patients treated with t-PA were at least 30 % more likely to have minimal or no disability at 3 months on the assessment scales”

“Symptomatic intra-cerebral haemorrhage within 36 hours after the onset of stroke occurred in 6.4 % of patients given t-PA but only 0.6 % of patients given placebo (P < 0.001). Mortality at three months was 17 % in the t-PA group and 20 % in the placebo group (P = 0.30).”

NINDS 1995
## NINDS - modified Rankin scores

### Table: Modified Rankin Scale at 3 months in NINDS rt-PA trial

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No symptoms at all</td>
</tr>
<tr>
<td>1</td>
<td>No significant disability despite symptoms. Able to carry out all usual duties and activities</td>
</tr>
<tr>
<td>2</td>
<td>Slight disability: unable to carry out all previous activities, but able to look after own affairs unassisted</td>
</tr>
<tr>
<td>3</td>
<td>Moderate disability: requiring some help but able to walk unassisted</td>
</tr>
<tr>
<td>4</td>
<td>Moderately severe disability: unable to walk and attend to own bodily needs unassisted</td>
</tr>
<tr>
<td>5</td>
<td>Severe disability: bedridden, incontinent and requiring constant nursing care and attention</td>
</tr>
<tr>
<td>6</td>
<td>Death</td>
</tr>
</tbody>
</table>

Data from reference 1. Modified Rankin Scale scores range from 0 (indicating no symptoms) to 6 (indicating death).

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NINDS 1995
Thrombolysis trials

European Co-operative Acute Stroke Study (ECASS I), 1995

620 patients, <6 hours of stroke onset. Randomised to rt-PA (1.1mg/kg) or placebo, 18-80 years.

“There was no difference in primary endpoints in the intention to treat analysis but the explanatory analysis of the target population showed a significant difference (p=0.035) in the Rankin Scale in favour of rt-PA treated patients”
Thrombolysis trials

European and Australian Co-operative Acute Stroke Study (ECASS II), 1998

800 patients, <6 hours of stroke onset. Randomised to rt-PA (0.9mg/kg) or placebo, 18-80 years.

“165 rt-PA patients and 143 placebo-group patients had favourable MRS outcomes (p=0.277). Outcomes were similar whether patients treated within 0-3 hours or 3-6 hours with no difference between treatment groups at day 90 +/-14 days”
Thrombolysis Registry

Safe Implimentation of Thrombolysis in Stroke Monitoring Study (SITS-MOST), 2007

6483 patients were recruited from 285 centres (50% with little previous experience in stroke thrombolysis) in 14 countries between 2002 and 2006 for this prospective, open, monitored, observational study.

“To compare the safety and efficacy of tissue plasminogen activator (rt-PA) administered in controlled clinical trials to that of rt-PA prescribed in routine clinical practice.”

(NB. All SITS-MOST patients were treated within the licence i.e within 3 hours of onset)
Thrombolysis Registry

SITS-MOST conclusion:

“Alteplase, when used in routine clinical practice, has a safety profile at least as good as seen in randomised controlled trials and is effective when used within 3 hours of stroke onset, even in stroke centres with little previous experience of thrombolytic therapy in acute stroke.”

“This trial showed a 3.4% improvement in direct comparison across the full modified Rankin scale at 3 months with other randomized clinical trials, which showed a 10% improvement for rt-PA use over placebo.”
SITS Database

Safe

Implementation of
Thrombolysis in
Stroke

SITS is an academic-driven, non-profit, international collaboration. It is an initiative by the medical profession to certify excellence in acute stroke treatment.

Internet-based interactive thrombolysis register, to serve as an instrument for clinical centres to follow their own treatment results and compare with other centres in their countries and in the collaborating countries.

www.acutestroke.org
Thrombolysis Registry

Evidence - On-going:

European Cooperative Acute Stroke Study (ECASS) III (Reporting - Vienna 2008)

To evaluate efficacy and safety of rt-PA between 3 and 4 hours after stroke onset in the European setting.

International Stroke Trial (IST3) (Reporting ? 2010/11)

To determine whether administration of rt-PA within 6 hours of ischemic stroke increases the proportion of independent survivors at 6 months.
Thrombolysis Benefit

Figure 2.2: Effect of Time to Thrombolysis on “Favourable Outcomes” at 3 months

Favourable outcome (mRS 0–1, Barthel index 95–100, NIHSS 0–1) at day 90
adjusted odds ratio with 95% CI by stroke onset to treatment time (OTT)
ITT population (N=2775)

SITS Databases

SITS Registries

- SITS - Global registry of all patients irrespective of time to treatment
- SITS-MOST - Registry is closed
- SITS-ISTR - In support of the Asian and far eastern countries licence applications. Patients treated within licence
Thrombolysis
Thrombolysis

Numbers Needed to Treat for Several Therapies

- Thrombolysis < 6 hours vs placebo in myocardial infarction (MI) to prevent 1 death = 33 (absolute risk reduction (RR) of 3%)
- rt-PA < 3 hours vs placebo to prevent poor outcome (mRS 2-6) based on NINDS alone = 8.4
- rt-PA < 3 hours vs placebo to prevent disability or death (mRS 3-6) based on NINDS, ECASS I+II = 7 (relative odds reduction of 45%)

Thrombolysis

Inclusion criteria

- Aged 18 - 80
- Ischaemic stroke with clearly defined time of onset
- Measurable neurological deficit
- Neuroimaging excluding haemorrhage
- Consent
Exclusion criteria

- Evidence of intracranial haemorrhage on pretreatment evaluation
- Suspicion of subarachnoid haemorrhage
- Recent intracranial surgery or serious head trauma or recent previous stroke
- History of intracranial haemorrhage
- Uncontrolled hypertension at time of treatment (e.g., >185mm Hg. systolic or >110 m Hg. diastolic)
- Seizure at the onset of stroke
- Active internal bleeding
Exclusion criteria (cont.)

- Intracranial neoplasm, arteriovenous malformation, or aneurysm.

- Known bleeding diathesis, including but not limited to
  - Current use of oral anticoagulants (e.g., warfarin) with elevated INR.
  - Administration of heparin within 48 hours preceding the onset of stroke and an elevated activated partial thromboplastin time (aPTT) at presentation.
  - Platelet count < $100 \times 10^9$ per litre.
Thrombolysis

Pharmacokinetics

- Rapidly cleared from plasma
  - Initial distribution phase half life <5 mins
  - Terminal elimination phase 40 mins

- If infusion stopped
  - 50% cleared from plasma within 5 mins
  - 80% cleared from plasma within 10 mins
**Thrombolysis**

**rt-PA (Actilyse) Mode of action**

- **t-PA (intravenous)**
  - Plasminogen → Plasmin
  - Fibrin → Fibrin degradation products

(Fibrin Depletion: < 40% at 4 hours
> 80% at 24 hours
normal levels by 36 hours)
Thrombolysis

Dosage

- 0.9mg/kg/body weight up to a maximum of 90mg
- Dilute with sterile water to 1mg/ml
- Give 10% of dose as bolus injection
- Give 90% as infusion over 1 hour
# Thrombolysis

<table>
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<tr>
<th>Stones</th>
<th>Lbs</th>
<th>Kg</th>
<th>Bolus</th>
<th>Infusion</th>
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Post- Thrombolysis
Post-thrombolysis

First 24hrs of Care:

- Stroke nurse / medic must be present from infusion to safe transfer to ASU
- Thrombolysis observations for 24 hrs as per pathway
- 24-36 hrs repeat CT scan
- No antiplatelets for 24 hrs
- No IM injections (48hrs), catheterisation or invasive procedure (36hrs) - unless unavoidable
- IV access
Post-thrombolysis

What goes wrong:

- Early intra-cerebral haemorrhage
- Deteriorating conscious level due to oedema from infarct (but cannot distinguish from haemorrhage clinically)
- Other bleeding (unusual)
- Hypertension (>185/110mmHg)
- Anaphylaxis
Post-thrombolysis

Pulse, BP, O₂ saturation and conscious level:

- Every 15 mins for the first 2 hours (manual BP)
- Every 30 mins for the next 6 hours (automatic BP) = 8 hrs
- Hourly for further 12 hours = 20 hrs
- 2 hourly for 18 hrs = 38 hrs total
- Then 4 hourly (NB - Neurological observations done at same time as BP)

This is to detect hypertension, hypotension, bleeding or early neurological deterioration. (NB. If ICH, BP goes up and pulse goes down)

Post-thrombolysis

High blood pressure (target maximum BP <185/110mmHg)
If above this range

- Inform Dr if any single reading >230/120mmHg
- Check for pain and treat cause
- Recheck after 5 minutes.
- If BP 230/120mmHg on single reading or >185/110mmHg on two readings 5 minutes apart, suggested management is:
  - Nitrate infusion according to BP (local protocol)
  - Labetalol 10mg IV repeated 10-20 minutes (may mask bradycardia as early sign of raised intracranial pressure)
Post-thrombolysis

**Low blood pressure** (target minimum systolic BP >95mmHg)

*If below this range*

- Stop nitrate infusion
- Check for external bleeding
- Recheck after 5 minutes.
- If BP still below range, suggested management is:
  - Inform Dr
  - Give IV fluids as appropriate (local protocol)
  - Urgent blood for FBC and clotting
Post-thrombolysis

$O^2$ Saturations (target minimum 95%)

If lower than this level:

- Sit Patient up
- Supplementary $O^2$ as necessary
- Inform Dr
Post-thrombolysis

Conscious level (a ↓ of 2 points or more - taken as significant)
If conscious level score drops by this much, or other reason to suspect neurological deterioration then:

- Stop infusion
- Inform Dr
- Check clotting
- Consider repeat CT scan
- Consider cryoprecipitate
Post-thrombolysis

Decreased GCS, signs of raised intracranial pressure / intracranial bleeding:

- Unequal pupils
- Drop in consciousness
- Drowsiness
- Nausea, vomiting, sometimes photophobia
- Raising BP & falling pulse
Suspicion of intracranial haemorrhage
(headache, neurological deterioration reduced consciousness)

Stop r-TPA infusion if still active

Immediate non-contrast head CT

Immediate PT, aPTT, FBC, fibrinogen

Prepare 6-8 units cryoprecipitate

Prepare 6 units of platelets

Haemorrhage on CT?

Check laboratory results. Give cryoprecipitate and platelets. Notify neurosurgeons

Yes

No

Resume r-TPA infusion if suspended

Reperfusion After Thrombolysis

Left image: ACA, Collateral Flow from ACA, Occluded MCA

Right image: ACA, Anastomoses, Reperfused MCA
Case Histories
Abbreviated prescribing information (UK, STROKE ONLY)

ACTILYSE

Read the SPC before prescribing. Actilyse vials contain alteplase (recombinant human tissue-type plasminogen activator, rt-PA) dry powder 50mg, 20mg, or 10mg. **Indications:** acute ischaemic stroke, within 3 hours of symptom onset; exclude intracranial haemorrhage. **Dosage and Administration:** Give as soon as possible. Total dose 0.9 mg/kg (maximum 90mg): 10% by iv bolus, remainder by iv infusion over 60 minutes. Avoid aspirin or iv heparin in the 24 hours after treatment with Actilyse. **Contra-indications:** Hypersensitivity to any constituent and situations with a high risk of haemorrhage such as: significant bleeding disorder at present or within past 6 months; known haemorrhagic diathesis; concomitant oral anticoagulants; manifest or recent severe or dangerous bleeding; known history of or suspected intracranial haemorrhage; suspected subarachnoid haemorrhage or condition after subarachnoid haemorrhage from aneurysm; history of CNS damage; within 10 days of traumatic external heart massage, obstetrical delivery, recent puncture of a non-compressible blood-vessel; severe uncontrolled arterial hypertension; bacterial endocarditis, pericarditis; acute pancreatitis; documented ulcerative gastrointestinal disease during the last 3 months, oesophageal varices, arterial aneurysm, arterial/venous malformations; neoplasm with increased bleeding risk; severe liver disease, including hepatic failure, cirrhosis, portal hypertension and active hepatitis; major surgery or significant trauma in past 3 months; symptom onset more than 3 hours or unknown; minor neurological deficit or symptoms rapidly improving before infusion start; severe stroke; seizure at onset of stroke; evidence of ICH on CT-scan; symptoms of subarachnoid haemorrhage even if CT-scan normal; heparin within previous 48 hours and elevated thromboplastin time; history of stroke and concomitant diabetes; prior stroke within last 3 months; platelet count <100,000/mm3; systolic blood pressure >185 or diastolic >110 mm Hg, or aggressive management necessary to reduce BP to these limits; blood glucose <50 or >400mg/dl; for age 18-80 years only. **Precautions:** The elderly; situations where there is an increased risk of bleeding, including recent small traumas. Avoid rigid catheters. Treatment must be performed only by a physician trained and experienced in neurological care and in the use of thrombolytic treatments, with the facilities to monitor. Risk of intracranial haemorrhage is increased in this indication, particularly in patients with high risk of haemorrhage; small asymptomatic aneurysms of the cerebral vessels; pre-treatment with aspirin. Treatment should not be initiated later than 3 hours after the onset of symptoms. Monitor BP, give iv antihypertensive treatment if systolic BP>180mmHg or diastolic BP>105 mmHg.
**Interactions:** Coumarin derivatives, oral anticoagulants, platelet aggregation inhibitors, heparin, GPIIb/IIIa antagonists and other agents influencing coagulation increase haemorrhage risk. Concomitant treatment with ACE inhibitors may enhance the risk of an anaphylactoid reaction. **Pregnancy and lactation:** Experience is very limited; studies in animals have shown reproductive toxicity. It is not known if alteplase is excreted into breast milk. **Side-effects:** Very common (>1/10): Bleeding is the most frequent adverse reaction; bleeding from damaged blood vessels. Recurrent ischaemia/angina, hypotension and heart failure/pulmonary oedema; reperfusion arrhythrias. Common (>1/100 and ≤ 1/10): Symptomatic intracranial haemorrhage represents the major adverse reaction in acute ischaemic stroke (up to 10% patients) - discontinue Actilyse if potentially dangerous haemorrhage occurs, respiratory tract haemorrhage, gastrointestinal haemorrhage, ecchymosis, urogenital haemorrhage. Cardiac arrest, cardiogenic shock, reinfarction, nausea, vomiting, body temperature increased. Uncommon (>1/1,000 and ≤ 1/100): Haemopericardium, retroperitoneal haemorrhage, hypersensitivity/anaphylactoid reactions, mitral regurgitation, pulmonary/other systemic/cerebral/thrombotic embolism, ventricular septal defect. Rare (>1/10,000 and ≤ 1/1,000): Bleeding in parenchymatous organs, fat embolism. Very rare (≤1/10,000): Eye haemorrhage, serious anaphylaxis, events related to the nervous system - often associated with ischaemic/haemorrhagic cerebrovascular events. See SPC for other undesirable effects. **Presentations** and basic NHS prices: all packs contain appropriate quantity of water for injections; 1 x 50mg Actilyse + transfer device £300.00; 1 x 20mg Actilyse + transfer device £180.00; 1 x 10mg Actilyse £135.00. Actilyse PL 00015/0120. Water for injection PL 00015/0127. POM. Product Licence holder: Boehringer Ingelheim Ltd., Ellesfield Avenue, Bracknell, RG12 8YS. Further information available on request. See SPC for use in acute MI and acute PE. Date of preparation: January 2008

Adverse events should be reported to Boehringer Ingelheim Drug Safety on 0800 328 1627 (freephone). Information about adverse event reporting can be found at [www.yellowcard.gov.uk](http://www.yellowcard.gov.uk)
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