Stroke Thrombolysis Guidelines
Version 2.0 (March 2015)

Contents

ESC level of evidence given where available

TIME IS BRAIN

Work quickly and effectively. Aim door to needle < 60 minute (class 1 Level A).

NAME.	
D.O.B.	
HOSP. No	

DATE		**BLOODS TAKEN AT**	
ONSET TIME		**CT SCAN AT**	
ADMISSION TIME		**DRUG AT**	

ON ARRIVAL IN EMERGENCY DEPARTMENT	
If approximate onset time is < 4 hour. Take blood for urgent. FBC, U&E, GLUCOSE, CLOTTING & GROUP + HOLD. Ensure that Responsible Consultant is aware that the patient may be suitable for thrombolysis Speak to the on call radiologist to request an urgent C.T. Scan and CTA if available. Record baseline observations and commence continuous monitoring	**[ ]** **[ ]** **[ ]** **[ ]** **[ ]**
WITHIN 30 MINUTES OF ARRIVAL	
Determine definite onset time. A word of caution with right sided strokes (i.e. left hemiparesis etc.) they can be unreliable with time of onset and don't appreciate early signs of stroke. Get collateral if possible If collateral is not immediately available from the patient or relative contact the person who contacted the GP or ambulance service. <u>IF NECESSARY SPEAK TO THE GP OR AMBULANCE CREW.</u> Confirm that consent can be obtained Check availability of rt-PA Insert 18G I.V. Cannulae into both arms.	**[ ]** **[ ]** **[ ]** **[ ]** **[ ]** [ ] [ ]
WITHIN 45 MINUTES OF ARRIVAL	
Chase blood results Record NIHSS, Pre stroke Rankin and Barthel Confirm that the patient meets all of the inclusion and none of the exclusion criteria. Calculate dose of rt-PA from either actual or estimated body weight. (See weight / dose chart overleaf)	**[ ]** **[ ]** **[ ]** **[ ]**
FOLLOWING DRUG ADMINISTRATION	
Complete assessment details, ensure N.I.H. and Rankin are recorded in notes Check that the following information has also been recorded in the patients notes: Name of the Doctor obtaining verbal consent / assent Name(s) of the Doctors responsible for reading C.T. Scan Dosage of rt-PA given	**[ ]** **[ ]** **[ ]** [ ]
Urgent Intracranial and/or Extracranial CT angiogram (or MR angiogram) if available is recommended unless known severe renal failure or contrast allergy.	**[ ]**

THROMBOLYSIS with IV rt-PA: INCLUSION / EXCLUSION CRITERIA

Inclusion Criteria – Answers to ALL questions must be YES

		Yes	No
1.	Clinical diagnosis of ischaemic stroke causing a measurable neurological deficit - language, motor function, cognition, gaze, vision and/or neglect. Symptoms must be distinguishable from an episode of generalised ischaemia (i.e. syncope, seizure, or migraine)		
2.	Onset of symptoms within 4.5 hours prior to initiation of IV thrombolysis treatment (class 1, level A)		
3.	C.T scan appearances consistent with acute ischaemic stroke / normal CT		
4	Risks and benefits explained to patient or relative		

Exclusion Criteria Absolute Contraindications – Answers to ALL questions should be NO

1.	Symptoms of ischaemic stroke began > 4.5 hours prior to infusion start or time of symptom onset unknown.		
2.	Unconscious patient in the setting of an anterior circulation stroke. For basilar thrombosis, this is not a contraindication		
3.	Active colitis, Active peptic ulcer disease, Severe liver disease, incl. hepatic failure, portal hypertension, oesophageal varices; Active hepatitis; Extensive angiodysplasia		
4.	Uncontrolled hypertension persistently systolic > 180mmHg or diastolic > 105mmHg		
5.	Symptoms suggestive of subarachnoid haemorrhage, even if the CT scan is normal.		
6.	Infective endocarditis, pericarditis or presence of ventricular aneurysm related to recent myocardial infarction < 1/12		
7.	Intra-spinal surgery $\leq$ 3 months		
8.	Lumbar puncture within 7 days		
9.	Uncorrected Blood Glucose <3 mmol/L. Review 10 mins post treatment of hypoglycaemia		
10.	Hypersensitivity to rt-PA (Alteplase) or its components		
11.	AVM especially if large and on same side of brain		
	Risk of Bleeding		
12.	Hereditary or acquired bleeding disorder		
13.	Recent severe / dangerous bleeding from the gastrointestinal or urinary tract in last 21 days, Recent unexplained drop in haemoglobin		
14.	Platelet count <100 x 10^9/L		
15.	Current anticoagulant therapy with warfarin, unless INR < 1.7. (If INR 1.4-1.7 ,should be carefully considered)		
16.	Novel anticoagulants within the last 48 hours if normal renal function, and longer if renal impairment and elevated sensitive laboratory tests such as APTT, INR, ECT, TT or appropriate anti-factor Xa activity assays. Consider clot retrieval – see P5		
17.	Administration of therapeutic heparin within the previous 48 hours with elevated APTT ratio, or low molecular weight heparin (LMWH) within 36 hours. Anti-factor Xa activity might be available if on LMWH. See p 5		
	Relative Contraindications – Where answer is Yes, discuss with stroke consultant on-call		
18.	Minor neurological deficit (NIHSS $\leq$ 4) (but may benefit individual cases with low NIHSS e.g. dysphasia, hemianopia)		
19.	Symptoms rapidly improving before infusion starts (> 50% NIHSS improvement). Consider if CTA / MRA shows large vessel occlusion		
20.	C.N.S surgery or significant stroke within the previous 3 months		
21.	Trauma with internal injuries, surgery or visceral biopsy < 2 weeks; Traumatic external heart massage < 10 days.		
22.	Known history of spontaneous intracranial haemorrhage, especially if cause is untreated		
23.	Acute pancreatitis; Cirrhosis		
24.	Abdominal aortic aneurysm if no concern about active bleeding or recent increasing size		
25.	Pre- stroke Rankin $\geq$ 4		
26.	Seizure at stroke onset - caution because impairments may be secondary to post-ictal phenomenon rather than stroke (class IIa, C)		
27.	Recent puncture of a non-compressible blood vessel (e.g. subclavian or jugular vein puncture, if not mechanically sealed) or arterial puncture (excluding radial artery) within last 7 days		
28.	Active proliferative retinopathy; Confirmed recent (< 1 month) retinal haemorrhage – discuss with Ophthalmologist		
29.	Neoplasm with increased bleeding risk		
30.	Caution if Myocardial infarction < 1/12		
31.	Any history of central nervous system damage (i.e. neoplasm, aneurysm, intracranial or spinal surgery)		
32.	Peritoneal dialysis or haemodialysis		
33.	Previous Stroke AND Diabetes -treat if benefit felt to outweigh risks in individual cases		
34.	Pregnancy, or childbirth within the previous 4 weeks		
35.	rt-PA may be administered in selected patients under 18 years, although outside the current European Licence (class III, Level C)		

C.T CAUTION Checklist. Stroke Consultant on-call should discuss these with Radiologist

1.	High density lesion consistent with intracranial haemorrhage –	absolute contraindication		
2.	Hypodensity in >1/3 M.C.A.territory or equivalent (e.g. ASPECTS < 7) – balance benefit versus risks	relative contraindication		
3.	Extensive CT changes of evolving infarction or mass effect on CT	absolute contraindication		

BODY WEIGHT/DOSE CHART FOR rt-PA
(Actilyse)

Body Weight (Stones)	Body Weight (Kg)	Total rt-PA Dose (mg)	10% Bolus (ml)	90% IV Infusion (ml/hr)	No. of 50mg rt-PA vials needed
6st 4	40	36	4	32	1
6st 8	42	38	4	34	1
7st	44	40	4	36	1
7st 3	46	41	4	37	1
7st 7	48	43	4	39	1
7st 12	50	45	5	40	1
8st 2	52	47	5	42	1
8st 6	54	49	5	44	1
8st 12	56	50	5	45	2
9st 1	58	52	5	47	2
9st 6	60	54	5	49	2
9st 10	62	56	6	50	2
10st	64	58	6	52	2
10st 5	66	59	6	53	2
10st 9	68	61	6	55	2
11st	70	63	6	57	2
11st 4	72	65	6	59	2
11st 9	74	67	7	60	2
12st	76	68	7	61	2
12st 3	78	70	7	63	2
12st 8	80	72	7	65	2
12st 12	82	74	7	67	2
13st 3	84	76	8	68	2
13st 7	86	77	8	69	2
13st 12	88	79	8	71	2
14st	90	81	8	73	2
14st 6	92	83	8	75	2
14st 11	94	85	8	77	2
15st 2	96	86	9	77	2
15st 7	98	88	9	79	2
15st 10	100	90	9	81	2

DRUG DOSAGE AND ADMINISTRATION.

PATIENTS MUST BE *CONTINUOUSLY MONITORED* PRIOR TO AND DURING DRUG ADMINISTRATION, and for at least 24 hours following administration.

1. **Total dose: 0.9mg/kg. *MAXIMUM DOSE IS 90 MG.*** (See body weight/dose chart)
2. 10% of total dose given as an I.V. push over 2 minutes **supervised by a Doctor experienced in stroke thrombolysis**
3. **Give remaining 90%** of dose I.V over **60 minutes** via **infusion pump.**
4. **Observe** patient for any **deterioration during infusion.**

Interventional Thrombectomy (New RCT evidence available)

Recent trials - MR CLEAN[1], ESCAPE[2], EXTEND-IA[3], SWIFT-PRIME have shown a positive benefit towards thrombectomy in selected patients.
Each patient with the criteria below should be discussed with the local interventional neuro-radiologist on call.

Indications for Discussion with Neuro-Radiology Centre

1. Clinical examination consistent with acute ischaemic stroke.
2. Non contrast CT brain showing no infarct or evidence of early acute small core infarct (ASPECTS >4)
3. CTA if available showing large vessel occlusion
   (Intracranial or extracranial ICA, M1 or M2 middle cerebral or basilar artery).
4. Suitable or unsuitable for IV thrombolysis. If suitable, start immediately but do not wait to see the effect before calling neuroradiology.

The time frame < 6 hours from last known well, but a time frame of up to 12 hours was occasionally used in the ESCAPE.
Patients with a basilar artery occlusion (not included in above trials) can be considered up to 24 hours, and occasionally longer if stuttering symptom onset.

Modified Rankin Scale

SCORE	DESCRIPTION
0	No symptoms at 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 and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

Schedule from admission to hospital:

Pulse, BP, Oxygen saturations, temperature and Glasgow Coma Scale.	
All Strokes	Every 15 minutes for first hour Hourly for 4 hours 4 hourly for 24 hours.
During rt-PA	Every 15 minutes
Post rt-PA	Every 15 minutes for first hour Every 30 minutes for 6 hours Hourly for 17 hours.
Capillary glucose	
Admission and 4 hourly if abnormal or diabetic.	
12 hourly if normal and non diabetic.	
ECG	
Continuously for 24 hours.	

Guideline for Patients on heparin prior to the Stroke

Unfractionated heparin and normal APPT – no contra-indication to thrombolysis
LMWH at thromboprophylactic dose given > 12 hours earlier – no contra-indication to thrombolysis
LMWH – therapeutic dose with or without elevated APTT within 36 hours: Anti-factor Xa activity may be available, and help guide treatment with expert Haematologist input, but if not available, TPA treatment is contraindicated.

Blood Pressure Control Before, During and After rt-PA Treatment (Table 1)
• **If BP > 180mmHg and or diastolic BP >105mmHg. Aim systolic B.P. < 160mmHg**
• Weigh up risks and benefits as risk of symptomatic ICH will increase with high blood pressure
○ Labetalol 10mg IV over 1-2 mins. May repeat or double every 10mins to max of 300mg; or give initial dose then infusion at 2-8 mg/min. Monitor BP every 5 minutes during labetalol treatment. **OR**
○ Glyceryl trinitrate IV starting as 5-10mcg/min and titrated according to effect. ○ GTN patch 5 mg topically (which can be increased to 10mg if required) however onset of action time is up to 30 mins, with a peak effect at 2 hours. **OR**
○ Nicardipine 5mg/hour IV infusion, may increase by 2.5 mg/hour every 5 mins to max 15 mg/hour **OR**
○ Sodium nitroprusside 0.5mcg/kg/min infusion

STOP the rt-PA infusion if:

- Anaphylaxis
- BP systolic <100 mmHg
- BP systolic rises to >180/105 mmHg sustained after 5 minutes, or associated with neurological deterioration of any sort
- Major systemic bleeding
- Neurological deterioration of 2 points on GCS

Avoid the following procedures if possible

AVOID Arterial puncture (e.g. for ABGs) or central line for 24 hours	**Ensure adequate compression applied after any of these procedures**
AVOID IM injection for 24 hours unless justified by threat to life (e.g. anaphylaxis)	
AVOID Venepuncture for 12 hours unless clear clinical indication	
AVOID suctioning whenever possible, caution giving mouth care.	
AVOID NG tubes for 24 hours	

Indications for urgent CT scan following thrombolysis in acute ischaemic stroke patients

- Signs and Symptoms of **intracerebral haemorrhage or cerebral oedema/infarct swelling**
  - New or worsening severe headache.
  - Acute hypertension
  - Nausea and vomiting
  - Agitation
  - Seizure
- **Neurological deterioration**
  - Glasgow Coma Score drops by two or more points.
  - NIHSS rises by more than 4 points
  - New motor signs contralateral to the stroke
- Discuss concerns immediately with Consultant Stroke Physician.
- Contact on call Haematologist for advice regarding the reversal of rt-PA if CT scan confirms bleeding.
- However, many causes of neurological deterioration following thrombolytic therapy are not due to intracerebral haemorrhage.

Bleeding Risk

Individual risk factors for symptomatic intracerebral haemorrhage or risk scores have poor predictive ability. In isolation, rt-PA should not automatically be withheld on the basis of same.

Independent risk factors for symptomatic Intracerebral haemorrhage post thrombolysis

- Baseline symptom severity
- National Institute Neurological Disease Severity (NINDS) protocol violations

The following are not evidence-based but are surrogate markers for more severe strokes:

- Elevated serum glucose
- History of diabetes
- Advanced age
- Smoker
- Increased time to treatment
- Previous aspirin use
- High systolic blood pressure
- Low platelet count
- History of congestive cardiac failure
- Large baseline diffusion weighted imaging (DWI) lesions on (MRI) with early reperfusion

Post STROKE Thrombolysis Care

General management

- Pulse oximetry - maintain O2 saturations above 95%.
- Maintain normal temperature. Paracetamol if temp > 37^0C.
- Blood Glucose: Maintain blood glucose < 10 mmol/l using IV insulin if necessary.
- DVT prophylaxis –ideally with automates spontaneous compression devices.
- Mobilise in first 24 hours if tolerated
- Risks and benefits of all invasive procedures should be carefully considered..
- No urinary catheters for at least 1 hour after infusion ended if possible.
- Falls Risk Assessment & Prevention measures.
- No aspirin, clopidogrel, dipyridamole or anticoagulant (heparin, warfarin, NOAC's) for 24 hours.
- Hydration / Nutrition

A non-contrast CT brain should be performed 24-36 hours post thrombolysis for all patients. If no bleeding, Aspirin can be started.

Adverse events

1. Haemorrhage

- rt-PA is rapidly cleared from the plasma.
- Fibrinogen levels drop to <40% of normal at 4 hours after rt-PA administration.
- Fibrinogen levels return to 80% of normal by 24 hour after rt-PA administration.
- Bleeding after 36 hours is **rarely** due to rt-PA.
- Not all neurological deteriorations after rt-PA are due to haemorrhage. Neurological deterioration may be due to swelling of the infarct +/ contains a small amount of haemorhage
- Some patients who bleed after rt-PA deteriorate so dramatically that reversal is unlikely to change their outcome.
- Some patients have a haemorrhage on CT which is only found only on follow-up scanning at 24-36 hours when their neurological status has slowly deteriorated.

1A. Intracranial Bleeding

Occurs in 1 in 14 patients (~ 6%).
Suspect if

- New or worsening severe headache acute headache or worsening severity of headache.
- Acute hypertension > 180mmHg systolic BP, or >105mmHg diastolic BP
- Nausea and vomiting
- Agitation
- Seizure
- Glasgow Coma Score drops by two or more points.
- NIHSS rises by more than 4 points
- New motor signs contralateral to the stroke

Nursing Action

- Discontinue rt-PA infusion
- Immediate review from stroke registrar and inform consultant stroke physician

Medical Staff Action

- Assess airway, breathing and circulation
- Assess neurological state of patient
- Send blood for FBC, PT, APTT, fibrinogen, Group and save, TT (thrombin time – not available in all labs)
- Arrange immediate CT brain scan
- Inform Stroke Consultant.

If intracranial haemorrhage confirmed
Send CT via image-link / NIMIS to local Neurosurgical Unit and discuss case with neurosurgical registrar on call
Give

- Fibrinogen 4g (aim is for post-treatment fibrinogen level > 1.5 g/L) - If not available then give fresh frozen plasma 15mL/kg.
- Platelets 2 pools (= 10 units) - Platelets are given for platelet dysfunction and not thrombocytopenia as rt-PA can impair platelet function.

Consideration can be given to an anti-fibrinolytic agent i.e. Transexamic acid (1g bolus IV, followed by 1g IV over 30 minutes) after discussion with Haematology but only in extremis and if given early. It is no longer of value > 1-2 hours after discontinuation of rt-PA.

Of note, rt-PA may go on acting in the thrombus for many hours and fibrinogen or other therapeutically administered compounds may have little effect. Also, these patients are pro-thrombotic and there have been at least two cases of patients having myocardial infarction when given fibrinogen to reverse post-stroke thrombolysis bleeding status.
*Any hospital using this thrombolysis protocol should ensure Blood Bank have a stock of fibrinogen.

1B. Extra-Cranial Bleeding or bleeding into chest / abdomen / pelvis / bowel

Nursing action

- Discontinue rt-PA infusion
- Perform full set of observations
- Administer 15L O2 via non-rebreather mask
- Raise foot of bed if BP < 100 systolic.
- Immediate review from stroke registrar and inform consultant stroke physician

Action by medical staff

- Assess airway, breathing and circulation
- Apply direct pressure to external sources of bleeding
- Ensure two wide-bore IV lines present
- Send blood for FBC, U+E, Cr, pT, APTT, fibrinogen, Group and crossmatch
- Commence treatment with packed RBC **OR** if not yet available give 500mL crystalloid IV bolus

If life-threatening haemorrhage develops

- Activate "Code Red" massive transfusion protocol by notifying hematology laboratory
- Packed RBC must be started immediately as per Irish Blood Transfusion Service guidelines.
- Fibrinogen 4 g (aim is for post-treatment fibrinogen level > 1.5 g/L). If not available then give fresh frozen plasma 15mL/kg.
- Platelets 2 pools (= 10 units) - Platelets are given for platelet dysfunction and not thrombocytopenia as rt-PA can impair platelet function
- Tranexamic acid (1g bolus IV, followed by 1g IV over 30 minutes) can be used within one hour of haemorrhage onset. This should be discussed with haematology prior to use.

Discuss with specialist services to achieve haemostasis – these may include

- Haematology/General Surgery/Gastroenterology/Vascular surgery/Interventional Radiology

2. Anaphylaxis

Suspect anaphylaxis if there is

- Rapid onset of hypotension
- Urticarial rash (rapidly developing, red, blanching, often slightly raised)
- Lip, tongue or mouth swelling, new wheezing or breathlessness

Interventions

- Discontinue rt-PA infusion
- Assess and protect airway
- Elevate foot of bed
- Administer 15L O2 via non-rebreather mask
- Immediate review from stroke registrar and inform consultant stroke physician

Medical Staff Action

- Assess airway, breathing and circulation
- If lip or tongue swelling, give adrenaline 500 microgrammes IM (0.5mL of 1:1000 solution)
  - adrenaline IV should only be given by experienced specialists.
- Crystalloid 500mL bolus IV
- Hydrocortisone 200mg IV
- Chlorphenamine 10 mg IV
- Ensure two wide-bore IV lines present
- Send blood for FBC, U+E, Cr, PT, APTT, fibrinogen, Group and save.

<u>Orolingual Angioedema</u>

Acquired angioedema is a different condition to anaphylaxis. It is rarely a life-threatening condition.
Acquired angioedema is characterised by lip and tongue swelling, without hypotension or urticaria. The reaction is often contralateral to the ischaemic hemisphere. The risk is higher in patients taking ACE inhibitors, and with ischaemia of the insula and frontal cortex. If no other signs of anaphylaxis, rt-PA can be continued but need to observe closely

3. Hypotension

More frequent occurrence than anaphylaxis and may be transient.

Nursing Action

- Administer 15L O2 via non-rebreather mask.
- Elevate foot of bed

Medical Staff Action

- Assess airway, breathing and circulation.
- Check manually if in any doubt. Caution in atrial fibrillation- repeat.
- Send blood for FBC, U+E, Cr, pT, APTT, fibrinogen, Group and save.
- Administer 24% O2 even if normal sats.
- Consider drug effects
- Crystalloid0.9% saline 500mL bolus IV and monitor BP every 5 minutes. Consider pressor agents.
- Consider a mean arterial pressure (MAP) of 130mmHg in hypertensive and 110mmHG in normotensive patients- as autoregulation is lost in the ischaemic brain, a drop in blood pressure will reduce flow to the penumbral regions.

4. Hypertension - BP > 180/105mmHg post thrombolysis. (Aim < systolic BP <160mmHg)

- See Table 1 page 6

5. Seizure during rt-PA infusion

- Resuscitate & treat seizure
- Stop rt-PA infusion immediately
- Repeat CT scan - if no intracranial haemorrhage, Stroke Physician to decide whether to restart infusion

Management of Complications of all Stroke Patients

Any unexpected fall in GCS or increased drowsiness

- Immediately check and document Pulse, temp, BP, O2 sats, capillary glucose and ECG. Ask for medical review
- Consider intracereberal haemorrhage (especially if thrombolysed < 36 hours), haemorrhagic transformation, seizures, sepsis, dehydration, drug reaction, CCF, dysrhythmia, MI, DVT/PE, metabolic derangement, urinary retention etc.

Hypoxia (O2 saturation <95%)

- Check airway, reposition and suction
- if needed. Give O2 by mask or nasal cannulae and titrate to achieve sats >95%.
- If persistent and/or needing >24% O2, ask for urgent medical review.

Pyrexia

- Cool and remove clothing/bedclothes.
- Use fans/sponging/cooling blankets if necessary.
- Give paracetamol 1gm oral/pr.
- Implement Sepsis 6 protocols. Take cultures-blood, urine, sputum.

Abnormal capillary glucose

- <3 mmol/L - give glucose orally (50-100mls Lucozade).
- IV dextrose 50% if unable to give orally or hypostop IM.
- 3-4 mmol/L – check again in 10 minute
- s>15 mmol/L - ask for medical review. Need to consider insulin infusion.
- Continue to monitor capillary glucose closely.

Abnormal heart rate/rhythm

<50 or >120/minute, new irregular pulse:

- Perform immediate 12 lead ECG and ask for urgent medical review.

Brain Oedema or increased intracranial pressure (ICP)

Space-occupying brain oedema is a main cause of early deterioration and death in patients with large supratentorial infarcts. Life-threatening brain oedema usually develops between the 2nd and 5th day after stroke onset, but up to one third of patients can have neurological deterioration within 24 hours after symptom onset.

Malignant Middle Cerebral Artery Infarction

Large infarctions in the MCA territory may develop space-occupying brain oedema, leading to midline shift, raised ICP and herniation. This can occur especially in patients < 70 years. The clinical course is deterioration of consciousness, respiratory insufficiency and signs of brain stem herniation usually within 2 to 5 days. The mortality is 50-80%. Early identification of patients at risk is advised. Treatment should begin before herniation occurs. Dominant-hemisphere stroke patients may remain severely aphasic. Talk to family about quality of life after stroke survival versus death.

Predictors of increased risk of Malignant Middle Cerebral Infarction :

Clinical: History of hypertension, heart failure, elevated white cell count, coma on admission, nausea, vomiting or systolic BP > 180 mmHg within first 24 hours.

Radiological: Hyperdense MCA sign, > 50% MCA hypodensity, involvement of additional vascular territory, local brain swelling or midline shift.

Medical Therapy

- Head positioning at an elevation of up to 30 degrees to help venous drainage.
- Analgesia, avoid noxious stimuli, appropriate oxygenation and normalize body temperature
- Osmotic agents e.g. mannitol is first line medical treatment if clinical or radiological signs of space-occupying oedema. Use Mannitol 20% (i.e. 20g in 100mls). Give 1g/kg bolus, followed by 0.25g/kg over 20 – 30 minutes. Check serum osmolality every 12 hours and repeat 0.25g/kg dose every 6 hours as necessary for up to 24 hours. Max dose is 2g/Kg/day (level IV evidence).
- If serum osmolality > 320 mOsm/kg, the drug should be discontinued or reduced until osmolarity returns to normal. If mannitol is required more than every 3 – 4 hours / serum osmolality rises > 320mOsm/kg, yet ICP remains elevated, administration of more mannitol is likely to lead to renal failure, metabolic acidosis and death, and should be discontinued. An in-line 5micron filter should be used during administration. Mannitol may crystallise at low temp – redissolve by warming. Maximum reduction in ICP occurs within 60 – 90 minutes, and lasts up to 8 hours. Rebound cerebral oedema may occur however, within 12 hours.
- Mild hyperventilation, including those with herniation syndrome (Level IV)
- Thiopental as a bolus acts quickly, significantly reduces ICP and can be used to treat acute crisis
- Dexamethasone and Corticosteroids should not be given.
- Hypotonic and glucose-containing solutions should be avoided.

Decompressive surgery

Surgical decompressive therapy within 48 hours after symptom onset is recommended in patients < 60 years of age with evolving malignant MCA infarcts (Class 1, level A). A pooled analysis of 93 patients (DECIMAL, DESTINY and HAMLET trials) showed an increased survival (NNTs 2, 4, and 2 respectively) and mRS <4 or mRS < 3 compared with the control group at 1 year[4]. There was no increase in proportion of patients who survived surgery in a vegetative state (mRS 5). A systematic review of 12 observational retrospective studies showed that timing of surgery, side of infarct, signs of herniation before surgery and involvement of other vascular territories did not significantly affect outcome- formatting in this section to be edited – can't see end of 'showed'

At present, there is not enough evidence to make a recommendation regarding hemicraniectomy in those aged over 60 with malignant MCA infarction syndrome. The DESTINY II trial randomised 112 patients with malignant MCA infarction aged between 61 and 82 years to conservative management in the intensive care unit or hemicraniectomy[5]. A significant benefit of hemicraniectomy in terms of the primary endpoint, survival without disability, was demonstrated (Rankin ≤ 4, 38% of hemicraniectomy group versus 18% of control group, p= 0.04). However, there was also an increase in the proportion surviving with severe disability (Rankin 5, 28% versus 13%, respectively; Add P). Therefore, discuss each case with local Neurosurgeon.

Criteria for consideration of decompressive surgery or hemicraniectomy

- Age less than 60.
- NIHSS > 15
- Infarct signs on CT of ≥ 50% of MCA territory, or 145cm^3 infarct volume on DWI
- < 45 hours from onset (surgery should be undertaken < 48 hours from onset)
- >7.5mm midline shift; > 4 mm midline shift with lethargy

Surgical decompression is a treatment of choice for space occupying cerebellar infarcts that compress the brainstem although RCT's are lacking (Class III level C). Surgery should be performed before signs of herniation develop.
The prognosis among survivors can be very good even in patients who are comatose before surgery.

Early Ischaemic Changes in Acute Stroke[6-8]

- The non-contrast CT scan is still regarded as the most important assessment tool in the investigation of patients with suspected acute stroke.
- 5mm sections are preferred, but slice thickness must be < 10mm
- CT scanning should be performed no longer than one hour prior to initiation of thrombolysis
- Early treatment appears to be more critical to outcome from thrombolysis than the presence or absence of early ischaemic changes (EIC) on CT

Low density

- Loss of gray/white differentiation (focal or diffuse area in cerebral or cerebellar hemisphere)
- Loss of insular ribbon, obscuration of sylvian fissure
- Loss of basal ganglia
- Loss of lentiform nucleus

Brain swelling

- Loss of sulci / cortical sulcal effacement
- Effacement of ventricles
- Loss of definition of the basal ganglia
- Loss of insular ribbon

Hypodensity in > 1/3 of the middle cerebral artery (MCA) territory

Hypodensity is associated with the most severe reduction in cerebral blood flow and volume on perfusion imaging. Brain swelling without hypoattenuation is thought to be indicative of a more moderate or less prolonged hypoperfusion and potentially viable tissue.

Involvement of > 1/3 of MCA territory indicates early ischaemic involvement of 2 or more different lobes of the cerebral hemisphere and basal ganglia, plus insular cortex. Greater than 1/3 of the MCA territory has been found to be more specific for detection of important early infarction signs at CT within hours of stroke, whereas use of the ASPECTS score was more sensitive.

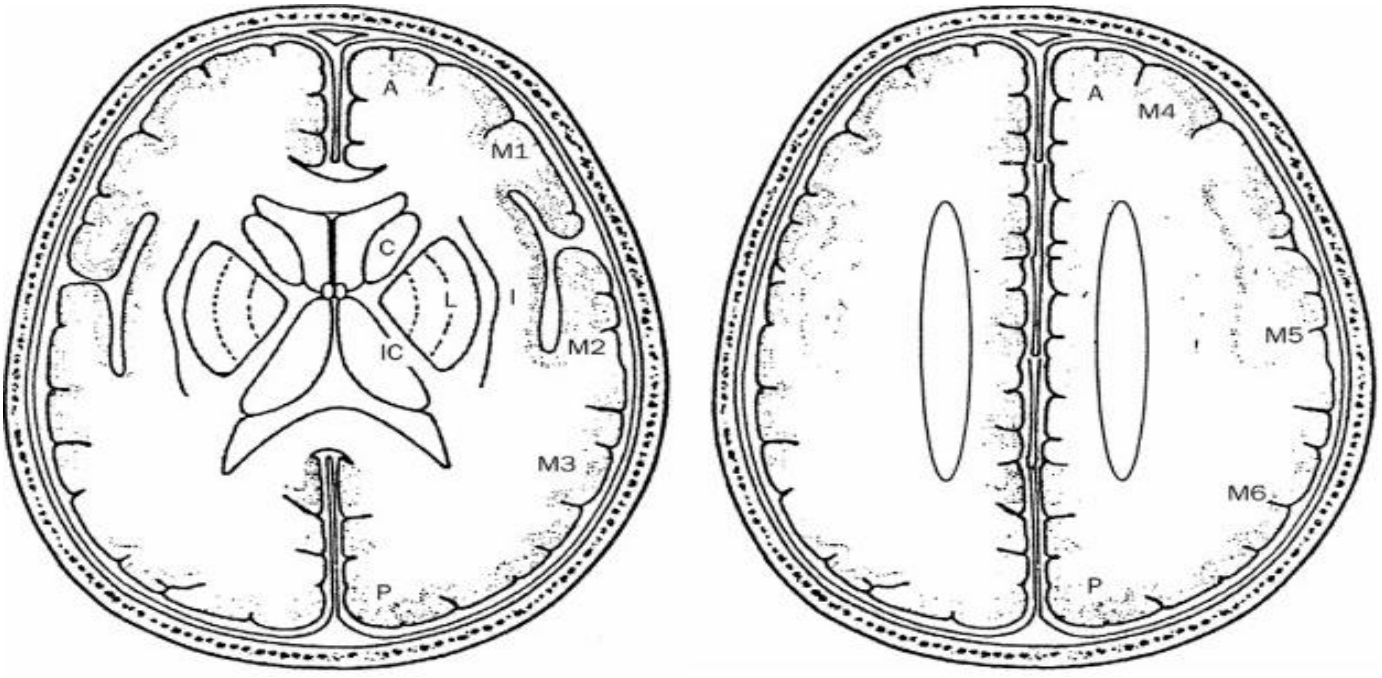
Hyperdense Artery – seen in MCA occlusion and basilar artery occlusion

Alberta Stroke Program Early CT (ASPECTS) score.

The purpose of this score is to help an evaluating clinician to systematically examine a CT scan of brain to identify early signs of ischaemia. It divides the Middle Cerebral Artery into 10 areas,

3 are sub-cortical; The Caudate Nucleus. **(C)**
The Lentiform Nucleus. **(L)**
The internal capsule (Genu and posterior limb only).**(IC)**

7are cortical; The insula. **(I)**
6 areas of cortex **M1-M6** are also scored.



Method of Scoring: A score of 1 is given for a normal region and 0 for a region showing signs of ischaemia. Only new areas of ischaemia are scored. A score of 10 implies no new signs of ischaemia. The lower the score, the more progressive ischaemic change. Hyperdense artery is recorded but not a component of the ASPECTS. The ASPECTS does not include anterior cerebral artery, posterior cerebral artery or basilar artery occlusion. Training is required for use of ASPECTS.

Evidence for intravenous thrombolysis in Ischaemic stroke

Thromboembolic occlusion leading to ischaemia accounts for 80% of strokes. There is evidence[9-15] suggesting that administering the thrombolytic agent, Recombinant Tissue Plasminogen Activator (rt-PA, Alteplase, Actilyse®) intravenously within 3 hours of symptom onset, to reperfuse blood vessels is effective in patients with acute ischaemic stroke. Evidence from these trials suggest a net benefit from rt-PA with approx. **1 fewer patient dead or dependent at 3 months per 10 treated.** This is based on administering rt-PA **within 3 hours from symptom onset within strict clinical and laboratory criteria**. ECASS-III trial found benefit in treating patients up to 4.5 hours, with a number need to treat (NNT) for a cure of 14[16]. Over 20 RCTs have been conducted in ischaemic stroke, treating > 5000 patients, using different thrombolytic agents.

Intravenous rt-PA has been licensed in Europe since 2002. It is subject to strict criteria to ensure safe administration as per the trial protocols which showed its benefit. The rate of cerebral haemorrhage is increased, but overall mortality is unchanged. The rate of haemorrhage is increased further by protocol deviations.

Numbers needed to treat (NNT)		
To cure if within 90 minutes	8	
To cure if within 3 hours	10	[17]
To cure if within 4.5 hours	14	
To derive some benefit	2-3	
Numbers needed to harm (NNH)		
To do worse	35	
To kill or leave permanently disabled	100	[18]

rt-PA (Alteplase) in acute stroke: Information for Patients

This leaflet contains information about rt-PA (alteplase) to treat acute stroke.

It tells you: How the medicine works
Whether there are any side effects

Why have I been given this leaflet?

The information in this leaflet will help you to remember what your doctor has told you about this medicine. It may also help you to decide whether you want to go ahead with this treatment.

What is rt-pA (alteplase) and how does it work?

Alteplase is a medicine which dissolves blood clots which are stopping the blood circulating. It is used routinely after heart attacks and it has now been shown to be effective in treating acute stroke. Alteplase is not able to dissolve all blood clots because they vary in size and strength. The sooner treatment with alteplase is started, the better the chance of a good recovery from the stroke. Alteplase treatment must be started within 4.5 hours of stroke symptoms coming on.

Alteplase is given through a drip into a vein in the arm. All patients who choose to have alteplase will be monitored very closely and will have a follow up brain scan 24-36 hours after the treatment. Otherwise, their care will be the same as for all other people who have had a stroke.

One in three patients will show some improvement with the drug and one in eight people will have a dramatic improvement. One in thirty five people will be worse after the drug and one in 100 will die or be left permanently disabled as a result of the drug in conjunction with their stroke.

When should alteplase not be used?

Alteplase should not be used when there is a high risk of bleeding. Tell your doctor if any of these conditions apply to you:
Severe liver disease
Diabetic with poor vision
Cancer
Bacterial endocarditis
Acute pancreatitis
Recent severe bleeding
Stomach or duodenal ulcers in the last 3 months
Any invasive medical procedure in the last 10 days
Any other condition that gives you a tendency to bleed
Major surgery or traumatic accident in the last 3 months
Taking drugs to thin the blood (e.g. warfarin tablets or heparin injections)

Are there any side effects?

Most medicines cause side effects. Alteplase treatment can sometimes cause bleeding, fever (high temperature), low blood pressure for a short time, nausea (feeling sick) and vomiting (being sick). Rarely, it causes seizures (fits) or allergic reactions.

Occasionally, bleeding into the brain happens after a stroke because the stroke has damaged blood vessels in the brain. **This can result in a bigger stroke or even death**. This bleeding happens more often if alteplase treatment is given. **In other words, alteplase increases the chance of bleeding into your brain in the short term but increases your chance of recovering fully from your stroke in the long term. Bleeding may also occur into the spinal cord and other organs.**

How can I find out more?

If you have any further questions or concerns, please speak your doctor.

Documentation should include:

- Time of onset, time of arrival, time of completion of work-up,
- Writing should be legible and signed
- Examination findings including NIHSS score
- Diagnosis and differential diagnosis
- Proposed treatment and why it should or should not be given
- Informed consent, potential benefits, potential risks and complications

Guidelines will change as the license for thrombolysis changes

Useful Addresses:

ASPECTS : **http://brainomix.com/strokeaspects.html**
European Stroke Organisation: www.eso-stroke.org
American Heart Association: www.americanheart.org
ISPGM: www.ispgm.ie

Writing Group

Dr. Rachael Doyle, St. Columcille's and St. Vincent's University Hospital
Dr. Ronan Collins, Adelaide and Meath Hospital Dublin, incorporating the National Children's Hospital
Professor Joe Harbison, St. James's Hospital
Dr. Dominick McCabe, Adelaide and Meath Hospital Dublin, incorporating the National Children's Hospital
Dr. Marie Therese Cooney, St. Columcille's and St, Vincent's University Hospital
Professor Sean Murphy, Mater Misericordiae University Hospital.
Prof David Williams, Beaumont Hospital
Dr. Christina Donnellan, South Tipperary General Hospital

Correspondence to: **Rachael.doyle@hse.ie**

Contributors

Irish Heart Foundation Council of Stroke representing

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Irish Consultants Neurologists' Association
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Faculty of Radiologists
Association of Emergency Medicine

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Disclaimer

This document is intended as a guideline only. An extensive literature search has been carried out and the guidelines follow current recommendations at time of publication and reflect a 'middle ground'. Training is required for administration of thrombolysis. The practise of thrombolysis in acute stroke is wide and varied and depends on local expertise. Trials in the area of thrombolysis are ongoing. Guidelines will change. Guidelines will not cover all complex clinical cases. The guidelines should be used with sound clinical judgement and treatment individualised to patients.

References:

1. Berkhemer OA, Fransen PS, Beumer D*, et al* for the MR CLEAN investogators*.* A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med 2015;**372**:11-20.
2. Goyal M, Demchuk AM, Menon BK*, et al* for the ESCAPE investigators*.* Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med 2015;**372**:1019-30.
3. Campbell BC, Mitchell PJ, Kleinig TJ*, et al* for the EXTEND 1A investigators*.* Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med 2015;**372**:1009-18.
4. Vahedi K, Hofmeijer J, Juettler E*, et al.* Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials. Lancet Neurol 2007;**6**:215-22.
5. Juttler E, Unterberg A, Woitzik J*, et al.* Hemicraniectomy in older patients with extensive middle-cerebral-artery stroke. N Engl J Med 2014;**370**:1091-100.
6. Wardlaw JM, Mielke O. Early signs of brain infarction at CT: observer reliability and outcome after thrombolytic treatment--systematic review. Radiology 2005;**235**:444-53.
7. Barber PA, Demchuk AM, Zhang J*, et al.* Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT Score. Lancet 2000;**355**:1670-4.
8. Demchuk AM, Hill MD, Barber PA*, et al.* Importance of early ischemic computed tomography changes using ASPECTS in NINDS rtPA Stroke Study. Stroke 2005;**36**:2110-5.
9. Hacke W, Kaste M, Fieschi C*, et al.* Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). JAMA 1995;**274**:1017-25.
10. Hacke W, Kaste M, Fieschi C*, et al.* Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. Lancet 1998;**352**:1245-51.
11. Clark WM, Wissman S, Albers GW*, et al.* Recombinant tissue-type plasminogen activator (Alteplase) for ischemic stroke 3 to 5 hours after symptom onset. The ATLANTIS Study: a randomized controlled trial. Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke. JAMA 1999;**282**:2019-26.
12. Clark WM, Albers GW, Madden KP*, et al.* The rtPA (alteplase) 0- to 6-hour acute stroke trial, part A (A0276g) : results of a double-blind, placebo-controlled, multicenter study. Thromblytic therapy in acute ischemic stroke study investigators. Stroke 2000;**31**:811-6.
13. Marler JR, Tilley BC, Lu M*, et al.* Early stroke treatment associated with better outcome: the NINDS rt-PA stroke study. Neurology 2000;**55**:1649-55.
14. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. N Engl J Med 1995;**333**:1581-7.
15. Hacke W, Donnan G, Fieschi C*, et al.* Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. Lancet 2004;**363**:768-74.
16. Hacke W, Kaste M, Bluhmki E*, et al.* Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med 2008;**359**:1317-29.
17. Saver JL. Number needed to treat estimates incorporating effects over the entire range of clinical outcomes: novel derivation method and application to thrombolytic therapy for acute stroke. Arch Neurol 2004;**61**:1066-70.
18. Saver JL. Hemorrhage after thrombolytic therapy for stroke: the clinically relevant number needed to harm. Stroke 2007;**38**:2279-83.