General Stroke Treatment

- Content
  - Monitoring
  - Pulmonary and airway care
  - Fluid balance
  - Blood pressure
  - Glucose metabolism
  - Body temperature

Monitoring

- Continuous monitoring
  - Heart rate
  - Breathing rate
  - O_2 saturation
- Discontinuous monitoring
  - Blood pressure
  - Blood glucose
  - Vigilance (GCS), pupils
  - Neurological status (e.g. NIH stroke scale or Scandinavian stroke scale)

Pulmonary function

- Background
  - Adequate oxygenation is important
  - Improve blood oxygenation by administration of > 2 l O_2
  - Risk for aspiration in patients with side positioning
  - Hypoventilation may be caused by pathological respiration pattern
  - Risk of airway obstruction (vomiting, oropharyngeal muscular hypotonia): mechanical airway protection

Blood pressure

- Background
  - Elevated in most patients with acute stroke
  - BP drops spontaneously during the first days after stroke
  - Blood flow in the critical penumbra passively dependent on the mean arterial pressure
  - There are no adequately sized randomised, controlled studies guiding BP management

Blood pressure

- Specific issues
  - Elevated BP (e.g. up to 200mmHg systolic or 110mmHg diastolic) may be tolerated in the acute phase of ischaemic stroke without intervention
  - BP may be lowered if this is required by cardiac conditions
  - Upper level of systolic BP in patients undergoing thrombolytic therapy is 180mmHg
  - Avoid and treat hypotension
  - Avoid drastic reduction in BP

Glucose metabolism

- Background
  - High glucose levels in acute stroke may increase the size of the infarction and reduce functional outcome
  - Hypoglycemia can mimic acute ischaemic infarction
  - Routine use of glucose potassium insulin (GKI) infusion regimes in patients with mild to moderate hyperglycaemia did not improve outcome[1]
- It is common practise to treat hyperglycemia with insulin when blood glucose exceeds 180mg/dl[2] (10mmol/l)

1: Gray CS et al.: Lancet Neurol (2007) 6:397-406
2: Langhorne P et al.: Age Ageing (2002) 31:365-71.

Body temperature

- Background
  - Fever is associated with poorer neurological outcome after stroke
  - Fever increases infarct size in experimental stroke
  - Many patients with acute stroke develop a febrile infection
- There are no adequately sized trials guiding temperature management after stroke
- It is common practice treat fever (and its cause) when the temperature reaches 37.5°C

General Stroke Treatment

Recommendations (1/4)

- Intermittent monitoring of neurological status, pulse, blood pressure, temperature and oxygen saturation is recommended for 72 hours in patients with significant persisting neurological deficits **(Class IV, GCP)**
- Oxygen should be administered if sPO_2 falls below 95% **(Class IV, GCP)**
- Regular monitoring of fluid balance and electrolytes is recommended in patients with severe stroke or swallowing problems **(Class IV, GCP)**

General Stroke Treatment

Recommendations (2/4)

- Normal saline (0.9%) is recommended for fluid replacement during the first 24 hours after stroke **(Class IV, GCP)**
- Routine blood pressure lowering is not recommended following acute stroke **(Class IV, GCP)**
- Cautious blood pressure lowering is recommended in patients with any of the following; extremely high blood pressures (>220/120 mmHg) on repeated measurements, or severe cardiac failure, aortic dissection, or hypertensive encephalopathy **(Class IV, GCP)**

General Stroke Treatment

Recommendations (3/4)

- Abrupt blood pressure lowering should be avoided **(Class II, Level C)**
- Low blood pressure secondary to hypovolaemia or associated with neurological deterioration in acute stroke should be treated with volume expanders **(Class IV GCP)**
- Monitoring serum glucose levels is recommended **(Class IV, GCP)**
- Treatment of serum glucose levels >180mg/dl (>10mmol/l) with insulin titration is recommended **(Class IV, GCP)**

General Stroke Treatment

Recommendations (4/4)

- Severe hypoglycaemia (<50 mg/dl [<2.8 mmol/l]) should be treated with intravenous dextrose or infusion of 10–20% glucose **(Class IV, GCP points)**
- The presence of pyrexia (temperature >37.5°C) should prompt a search for concurrent infection **(Class IV, GCP)**
- Treatment of pyrexia (>37.5°C) with paracetamol and fanning is recommended **(Class III, Level C)**
- Antibiotic prophylaxis is not recommended in immunocompetent patients **(Class II, Level B)**

Specific Stroke Treatment

- Content
  - Thrombolytic therapy
  - Early antithrombotic treatment
  - Treatment of elevated intracranial pressure
  - Prevention and management of complications

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
  - Several contraindications

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.

Thrombolytic Therapy (i.v. rtPA)

- Specific issues
  - A pooled analysis of the 6 i.v. rtPA trials confirms that i.v. thrombolysis may work up to 4.5 hours[1]
  - Caution is advised when considering i.v. rtPA in persons with severe stroke (NIHSSS>25), or if the CT demonstrates extended early infarcts signs
  - Thrombolytic therapy must be given by an experienced stroke physician after the imaging of the brain is assessed by physicians experienced in reading this imaging study[2]

1: Hacke W et al.: Lancet (2004) 363:768-74
2: Wahlgren N et al.: Lancet (2007) 369:275-82

Thrombolytic Therapy (i.v. rtPA)

- Specific issues
  - Factors associated with increased bleeding risk[1]
    - elevated serum glucose
    - history of diabetes
    - baseline symptom severity
    - advanced age
    - increased time to treatment
    - previous aspirin use
    - history of congestive heart failure
    - NINDS protocol violations
  - None of these reversed the overall benefit of rtPA

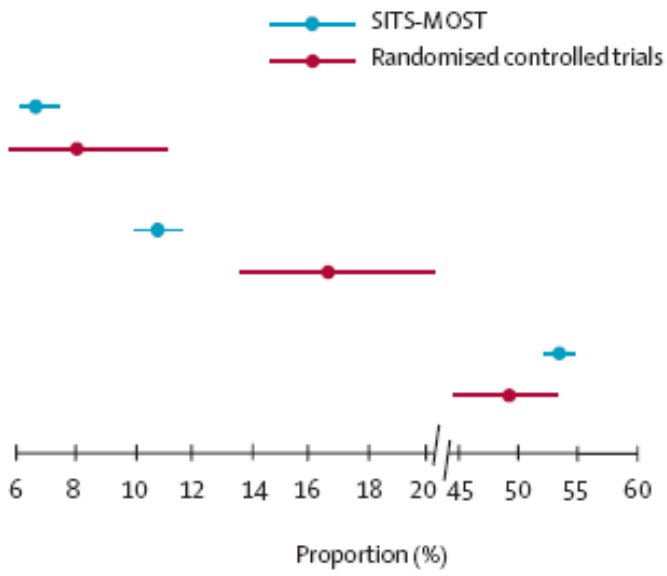
1: Lansberg MG et al.: Stroke (2007) 38:2275-8

Thrombolytic Therapy (i.v. rtPA)

Specific Treatment

Risk and outcome from 6,483 patients of the SITS-Most treated with iv-rtPA within a 3 hour time window[1]

	SITS-MOST Proportion (events/total; 95% CI)	Pooled randomised controlled trials* Proportion (events/total; 95% CI)
SICH per Cochrane/ NINDS definition†	7·3% (468/6438; 6·7–7·9)	8·6% (6·3–11·6)
Mortality within 3 months	11·3% (701/6218; 10·5–12·1)	17·3% (83/479; 14·1–21·1)
Independence (modified Rankin score 0–2) at 3 months	54·8% (3362/6136; 53·5–56·0)	49·0% (227/463; 44·4–53·6)



1: Wahlgren N et al.: Lancet (2007) 369:275-82

Thrombolytic Therapy (i.v. rtPA)

ECASS III

Intravenous rtPA administered between 3 and 4.5 hours (median3h59min) after the onset of symptoms significantly improves clinical outcomes patients with acute ischemic stroke compared to placebo.

More patients had a favorable outcome with rtPA than with placebo (52.4% vs. 45.2%; OR, 1.34; 95% CI, 1.02-1.76; P = 0.04).

In the global analysis, the outcome was also improved with rtPA as compared with placebo (OR, 1.28; 95% CI, 1.00 -1.65; P<0.05).

The incidence of intracranial hemorrhage was higher with alteplase than with placebo (for any intracranial hemorrhage, 27.0% vs. 17.6%; P = 0.001; for symptomatic ICH, 2.4% vs. 0.2%; P = 0.008).

Mortality did not differ significantly between the alteplase and placebo groups (7.7% and 8.4%, respectively; P = 0.68).

Hacke W, et al. New Engl J Med 2008;

Thrombolytic Therapy (i.v. rtPA)

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Hacke W, et al. New Engl J Med 2008;

Thrombolytic Therapy (i.v. rtPA)

- Mismatch based therapy
  - The use of multimodal imaging criteria may be useful for patient selection[1,2]
  - Available data on mismatch, as defined by multimodal MRI or CT, are too limited to guide thrombolysis in routine practice[3]
  - Data regarding the use of intravenous desmoteplase administered 3 to 9 hours after acute ischaemic stroke in patients selected on the basis of perfusion/diffusion mismatch are conflicting

1: Köhrmann M et al.: Lancet Neurol (2006) 5:661-7
2: Chalela J et al.: Lancet (2007) 369:293-298
3: Kane I et al.: JNNP (2007) 78:485-490

Thrombolytic Therapy (i.a.)

- Background: the use of i.a. rtPA, i.a. urokinase
  - Only cases and some prospective uncontrolled case series
- Facts: about use of i.a. pro-urokinase
  - Efficacy demonstrated in small RCT, 6h window[1]
  - Not approved and substance not available

1: Furlan A et al.: JAMA (1999) 282:2003-11

Specific Treatment

Recommendations (1/6)

- Intravenous rtPA (0.9 mg/kg BW, maximum 90 mg), with 10% of the dose given as a bolus followed by a 60-minute infusion, is recommended within 3 hours of onset of ischaemic stroke **(Class I, Level A)**
- Intravenous rtPA may be of benefit also for acute ischaemic stroke beyond 3 hours after onset **(Class I, Level B)** but is not recommended for routine clinical practice. The use of multimodal imaging criteria may be useful for patient selection **(Class III, Level C)**

Specific Treatment

Recommendations (2/6)

- Blood pressures of 185/110 mmHg or higher must be lowered before thrombolysis **(Class IV, GCP)**
- Intravenous rtPA may be used in patients with seizures at stroke onset, if the neurological deficit is related to acute cerebral ischaemia **(Class IV, GCP)**
- Intravenous rtPA may also be administered in selected patients over 80 years of age, although this is outside the current European labelling **(Class III, Level C)**

Specific Treatment

Recommendations (3/5)

- Intravenous rtPA (0.9 mg/kg body weight, maximum 90 mg), with 10% of the dose given as a bolus followed by a 60-minute infusion, is recommended within 4.5 hours of onset of ischaemic stroke **(Class I, Level A)**, although treatment between 3 and 4.5 h is currently not included in the European labelling.

Specific Treatment

Recommendations (4/6)

- Intra-arterial treatment of acute MCA occlusion within a 6-hour time window is recommended as an option **(Class II, Level B)**
- Intra-arterial thrombolysis is recommended for acute basilar occlusion in selected patients **(Class III, Level B)** Intravenous thrombolysis for basilar occlusion is an acceptable alternative even after 3 hours **(Class III, Level B)**

Antiplatelet therapy

- Background
  - Aspirin was tested in large RCTs in acute (<48 h) stroke[1,2]
  - Significant reduction was seen in death and dependency (NNT 70) and recurrence of stroke (NNT 140)
  - A phase 3 trial for the glycoprotein-IIb-IIIa antagonist abciximab was stopped prematurely because of an increased rate of bleeding[3]

1: International-Stroke-Trial: Lancet (1997) 349:1569-1581
2: CAST-Collaborative-Group: Lancet (1997) 349:1641-1649
3: Adams HP, Jr. et al.: Stroke (2007)

Anticoagulation

- Unfractionated heparin
  - No formal trial available testing standard i.v. heparin
  - IST showed no net benefit for s.c. heparin treated patients because of increased risk of ICH[1]
- Low molecular weight heparin
  - No benefit on stroke outcome for low molecular heparin (nadroparin, certoparin, tinzaparin, dalteparin)
- Heparinoid (orgaran)
  - TOAST trial neutral[2]

1: International-Stroke-Trial: Lancet (1997) 349:1569-1581
2: TOAST Investigators: JAMA (1998) 279:1265-72.

Neuroprotection

- No adequately sized trial has yet shown significant effect in predefined endpoints for any neuroprotective substance
- A meta-analysis has suggested a mild benefit for citocoline[1]

1: Davalos A et al.: Stroke (2002) 33:2850-7

Specific Treatment

EUROPEAN STROKE ORGANISATION

Recommendations (5/6)

- Aspirin (160–325 mg loading dose) should be given within 48 hours after ischaemic stroke **(Class I, Level A)**
- If thrombolytic therapy is planned or given, aspirin or other antithrombotic therapy should not be initiated within 24 hours **(Class IV, GCP)**
- The use of other antiplatelet agents (single or combined) is not recommended in the setting of acute ischaemic stroke **(Class III, Level C)**
- The administration of glycoprotein-IIb-IIIa inhibitors is not recommended **(Class I, Level A)**

Specific Treatment

Recommendations (6/6)

- Early administration of unfractionated heparin, low molecular weight heparin or heparinoids is not recommended for the treatment of patients with ischaemic stroke **(Class I, Level A)**
- Currently, there is no recommendation to treat ischaemic stroke patients with neuroprotective substances **(Class I, Level A)**

Elevated Intracranial Pressure

- Basic management
  - Head elevation up to 30°
  - Pain relief and sedation
  - Osmotic agents (glycerol, mannitol, hypertonic saline)
  - Ventilatory support
  - Barbiturates, hyperventilation, or THAM-buffer
  - Achieve normothermia
- Hypothermia may reduce mortality[1]

1: Steiner T et al.: Neurology (2001) 57(Suppl 2):S61-8.

Elevated Intracranial Pressure

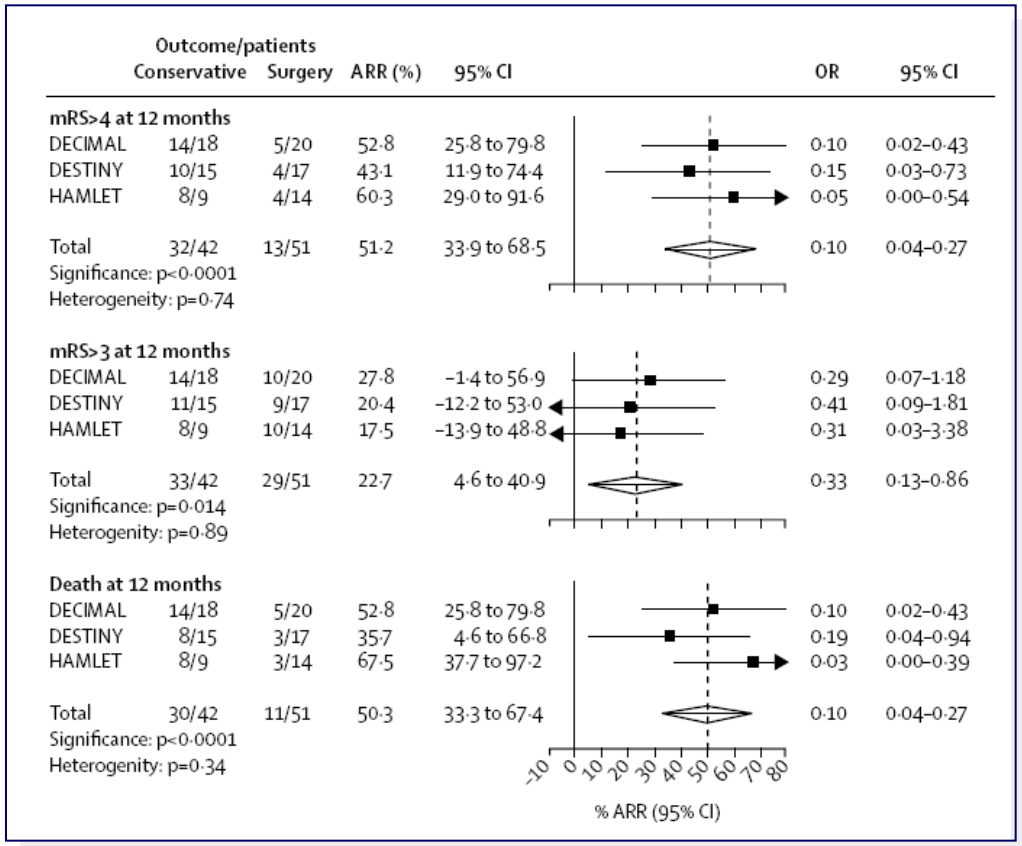
- Malignant MCA/hemispheric infarction
  - Pooled analysis of three European RCTs (N=93)[1,2]:
    - Significantly decreases mortality after 30 days
    - Significantly more patients with mRS ≤4 or mRS ≤3 in the decompressive surgery group after one year
    - No increase of patients surviving with mRS=5
  - Surgery should be done within 48 hours[1,2]
  - Side of infarction did affect outcome[1,2]
  - Age >50 years is a predictor for poor outcome[3]

1: Vahedi K et al.: Lancet Neurol (2007) 6:215-22
2: Jüttler E et al.: Stroke (2007) 38:2518-25
3: Gupta R et al.: Stroke (2004) 35:539-43

Elevated Intracranial Pressure

Specific Treatment

Absolute risk reduction (ARR) and odds ratio (OR) for unfavourable outcome at 12 months: combined analysis of decompression trials[1]



	Outcome/patients Conservative	Surgery	ARR (%)	95% CI	OR	95% CI
mRS>4 at 12 months						
DECIMAL	14/18	5/20	52·8	25·8 to 79·8	0·10	0·02–0·43
DESTINY	10/15	4/17	43·1	11·9 to 74·4	0·15	0·03–0·73
HAMLET	8/9	4/14	60·3	29·0 to 91·6	0·05	0·00–0·54
Total	32/42	13/51	51·2	33·9 to 68·5	0·10	0·04–0·27
Significance: p<0·0001						
Heterogeneity: p=0·74						
mRS>3 at 12 months						
DECIMAL	14/18	10/20	27·8	−1·4 to 56·9	0·29	0·07–1·18
DESTINY	11/15	9/17	20·4	−12·2 to 53·0	0·41	0·09–1·81
HAMLET	8/9	10/14	17·5	−13·9 to 48·8	0·31	0·03–3·38
Total	33/42	29/51	22·7	4·6 to 40·9	0·33	0·13–0·86
Significance: p=0·014						
Heterogenity: p=0·89						
Death at 12 months						
DECIMAL	14/18	5/20	52·8	25·8 to 79·8	0·10	0·02–0·43
DESTINY	8/15	3/17	35·7	4·6 to 66·8	0·19	0·04–0·94
HAMLET	8/9	3/14	67·5	37·7 to 97·2	0·03	0·00–0·39
Total	30/42	11/51	50·3	33·3 to 67·4	0·10	0·04–0·27
Significance: p<0·0001						
Heterogenity: p=0·34						

1: Vahedi K et al.: Lancet Neurol (2007) 6:215-22

Elevated Intracranial Pressure

Recommendations (1/2)

- Surgical decompressive therapy within 48 hours after symptom onset is recommended in patients up to 60 years of age with evolving malignant MCA infarcts **(Class I, Level A)**
- Osmotherapy can be used to treat elevated intracranial pressure prior to surgery if this is considered **(Class III, Level C)**

Elevated Intracranial Pressure

EUROPEAN STROKE ORGANISATION

Specific Treatment

Recommendations (2/2)

- No recommendation can be given regarding hypothermic therapy in patients with space-occupying infarctions **(Class IV, GCP)**
- Ventriculostomy or surgical decompression can be considered for treatment of large cerebellar infarctions that compress the brainstem **(Class III, Level C)**

Management of Complications

- Aspiration and pneumonia
  - Bacterial pneumonia is one of the most important complications in stroke patients[1]
  - Preventive strategies
    - Withhold oral feeding until demonstration of intact swallowing, preferable using a standardized test
    - Nasogastric (NG) or percutaneous enteral gastrostomy (PEG)
    - Frequent changes of the patient's position in bed and pulmonary physical therapy
  - Prophylactic administration of levofloxacin is not superior to optimal care[2]

1: Weimar C et al.: Eur Neurol (2002) 48:133-40
2: Chamorro A et al.: Stroke (2005) 36:1495-500

Management of Complications

- Urinary tract infections
  - Most hospital-acquired urinary tract infections are associated with the use of indwelling catheters[1]
  - Intermittent catheterization does not reduce the risk of infection
  - If urinary infection is diagnosed, appropriate antibiotics should be chosen following basic medical principles

1: Gerberding JL: Ann Intern Med (2002) 137:665-70c

Management of Complications

- Deep vein thrombosis and pulmonary embolism
  - Risk might be reduced by good hydration and early mobilization
  - Low-dose LMWH reduces the incidence of both DVT (OR 0.34) and pulmonary embolism (OR 0.36), without a significantly increased risk of intracerebral (OR 1.39) or extracerebral haemorrhage (OR 1.44)[1,2]

1: Diener HC et al.: Stroke (2006) 37:139-44
2: Sherman DG et al.: Lancet (2007) 369:1347-55

Management of Complications

- Pressure ulcer
  - Use of support surfaces, frequent repositioning, optimizing nutritional status, and moisturizing sacral skin are appropriate preventive strategies[1]
- Seizures
  - Prophylactic anticonvulsive treatment is not beneficial
- Agitation
  - Causal treatment must precede any type of sedation or antipsychotic treatment

1: Reddy M et al.: JAMA (2006) 296:974-84

Management of Complications

- Falls
  - Are common in every stage of stroke treatment
  - Risk factors include cognitive impairment, depression, polypharmacy and sensory impairment[1]
  - A multidisciplinary package focusing on personal and environmental factors might be preventive[2]
  - Exercise, calcium supplements and bisphosphonates improve bone strength and decrease fracture rates in stroke patients[3,4]

1: Aizen E et al.: Arch Gerontol Geriatr (2007) 44:1-12
2: Oliver D et al.: BMJ (2007) 334:82
3: Pang MY et al.: Clin Rehabil (2006) 20:97-111
4: Sato Y et al.: Cerebrovasc Dis (2005) 20:187-92

Management of Complications

- Dysphagia and feeding
  - Dysphagia occurs in up to 50% of patients with unilateral hemiplegic stroke and is an independent risk-factor for poor outcome[1]
  - For patients with continuing dysphagia, options for enteral nutrition include NG or PEG feeding
  - PEG does not provide better nutritional status or improved clinical outcome, compared to NG[2,3]

1: Martino R et al.: Stroke (2005) 36:2756-63
2: Dennis MS et al.: Lancet (2005) 365:764-72
3: Callahan CM et al.: J Am Geriatr Soc (2000) 48:1048-54

Management of Complications

Recommendations (1/4)

- Infections after stroke should be treated with appropriate antibiotics **(Class IV, GCP)**
- Prophylactic administration of antibiotics is not recommended, and levofloxacin can be detrimental in acute stroke patients **(Class II, Level B)**
- Early rehydration and graded compression stockings are recommended to reduce the incidence of venous thromboembolism **(Class IV, GCP)**
- Early mobilization is recommended to prevent complications such as aspiration pneumonia, DVT and pressure ulcers **(Class IV, GCP)**

Management of Complications

Recommendations (2/4)

- Low-dose s.c. heparin or low molecular weight heparins should be considered for patients at high risk of DVT or pulmonary embolism **(Class I, Level A)**
- Administration of anticonvulsants is recommended to prevent recurrent seizures **(Class I, Level A)**
- Prophylactic administration of anticonvulsants to patients with recent stroke who have not had seizures is not recommended **(Class IV, GCP)**
- An assessment of falls risk is recommended for every stroke patient **(Class IV, GCP)**

Management of Complications

Recommendations (3/4)

- Calcium/vitamin-D supplements are recommended in stroke patients at risk of falls **(Class II, Level B)**
- Bisphosphonates (alendronate, etidronate and risedronate) are recommended in women with previous fractures **(Class II, Level B)**
- In stroke patients with urinary incontinence, specialist assessment and management is recommended **(Class III, Level C)**
- Swallowing assessment is recommended but there are insufficient data to recommend a specific approach for treatment **(Class III, GCP)**

Management of Complications

Recommendations (4/4)

- Oral dietary supplements are only recommended for non-dysphagic stroke patients who are malnourished **(Class II, Level B)**
- Early commencement of nasogastric (NG) feeding (within 48 hours) is recommended in stroke patients with impaired swallowing **(Class II, Level B)**
- Percutaneous enteral gastrostomy (PEG) feeding should not be considered in stroke patients in the first 2 weeks **(Class II, Level B)**