Developments in the management of acute ischaemic stroke: implications for anaesthetic and critical care management

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Key points

Stroke is a major cause of death and disability.

Accurate classification of subtype allows prognosis to be more readily predicted.

Patients presenting within 4.5 h of acute ischaemic stroke should be considered for thrombolysis.

Patients under 60 yr of age with malignant middle cerebral artery territory infarction should be considered for decompressive hemicraniectomy.

Identifying which patients with acute ischaemic stroke are appropriate for critical care admission is difficult, and should be done in liaison with a stroke specialist.

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A stroke is defined by the WHO as a 'clinical syndrome consisting of rapidly developing clinical signs of focal (or global in case of coma) disturbance of cerebral function lasting more than 24 hours, or leading to death, with no apparent cause other than a vascular origin'. In this article, we will consider only ischaemic strokes.

Stroke is the third largest cause of death and the single biggest cause of disability in England. Each year ~110 000 people have a stroke (of which 80% will be ischaemic) with 20–30% dying within a month. It is estimated that 900 000 people alive in England today have suffered a stroke, approximately one-third of whom have moderate or severe disability.

Whilst stroke rates increase exponentially with age, three-quarters of strokes occur in people aged over 65.

This review will provide an overview of up-to-date stroke assessment, classification, and management including more recent advances, and also discuss the implications that more aggressive stroke management will have for critical care.

Stroke recognition tools

People developing a stroke need rapid recognition of their symptoms to enable timely treatment. Recognition tools have been developed for both pre-hospital and in-hospital assessment. In the UK, the National Institute for Health and Clinical Excellence (NICE) has recommended the use of the face, arm, speech test (FAST) by paramedics as a screening tool to increase the diagnostic accuracy. The test relies on a physical assessment for facial weakness, arm weakness, and speech disturbance, and yields a positive predictive value of ~80%.[1] Its weaknesses are that it does not take pre-existing disability into account and has a low sensitivity towards posterior circulation events and that stroke mimics may be FAST positive, e.g. Todd's paresis.

NICE also recommends that people admitted to the emergency department have their stroke diagnosis established rapidly, with the use of a validated recognition tool such as the 'Recognition Of Stroke In the Emergency Room' (ROSIER) tool. The ROSIER tool helps for a more detailed assessment including blood sugar measurement, visual field assessment and documentation of a history of seizures or loss of consciousness, and also focal neurological weakness and speech disturbance. It is more accurate than the FAST tool with a sensitivity of 93%.[1]

Classification[1,2]

Despite advances in neuro-imaging allowing easier localization of the ischaemic lesion, the recognition of stroke syndromes is important as it enables exclusion of stroke mimics, contributes to planning of investigations and direction of subsequent work-up, and allows clinicians to anticipate complications, predict prognosis, and order appropriate treatment. Several classification systems for stroke exist but the most commonly used is the Oxford Community Stroke Project (OCSP) classification (Bamford's classification), which recognizes four subtypes of stroke. These are outlined in Box 1 along with basilar artery thrombosis (a cause of posterior circulation stroke) and venous sinus thrombosis (a rare cause of stroke involving the venous channels of the brain).

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Box 1 Bamford's classification

Total anterior circulation syndrome (TACS) – all of:

- Unilateral motor, sensory deficit, or both affecting at least two of face, arm, and leg
- Higher cerebral dysfunction, e.g. dysphasia, dyspraxia, neglect, dyscalculia
- Homonymous hemianopia

If consciousness is impaired, higher cerebral dysfunction and visual field defects are assumed.

Partial anterior circulation syndrome (PACS):

- Two of the three components of TACS or pure higher cortical dysfunction or pure motor or sensory deficit not as extensive as for lacunar syndromes (see below).

Lacunar syndrome (LACS):

- Pure motor or pure sensory deficit affecting at least two of face, arm, or leg
- Sensorimotor deficit
- Ataxic hemiparesis
- Dysarthria, clumsy hand syndrome
- Acute onset movement disorder

Posterior circulation syndrome (POCS):

- Isolated hemianopia
- Brain stem signs
- Cerebellar ataxia

Prognosis varies significantly across the stroke subtypes with TACS carrying the worst prognosis (see Table 1).

Basilar artery thrombosis

Basilar artery thrombosis (BAT) is rare and generally carries a poor prognosis, although investigations such as magnetic resonance angiography (MRA) and computerized tomography angiography (CTA) have allowed identification of patients with partial or progressive occlusion who have limited ischaemia and better prognosis. BAT may be amenable to mechanical clot retrieval or intra-arterial thrombolysis.

Venous sinus thrombosis (VST)

Cerebral (dural) VST is uncommon, often affecting younger and middle-aged patients. NICE guidance is that patients with cerebral VST be treated with full-dose heparin anticoagulation initially, prior to commencement of warfarin therapy.[1]

Investigations

Blood tests are listed in Box 2.

Box 2 Routine blood tests

- Full blood count
- Clotting screen
- U+E
- Glucose
- Lipid profile
- ESR/CRP
- Thyroid function tests

Specialized assays: consider in individual cases especially during the work-up of a young patient:

- Vasculitis screen
- Thrombophilia screen (Protein C, Protein S, antithrombin III, factor V Leiden, antiphospholipid antibodies)
- Toxicology screen
- Homocysteine
- Serum lactate

Imaging tests[1,2]

Brain imaging: see Table 2

CT scanning: CT scanning remains the most commonly used imaging technique. Despite its relative insensitivity for the detection of early ischaemia, non-contrast CT is the imaging modality of choice in the acute phase because it is quick, available 24 h a

Table 1 Prognosis of main subtypes of acute ischaemic stroke

Stroke subtype	Outcome (%) at 30 days		Outcome (%) at 1 yr	
	Dead	Independent	Dead	Independent
Total anterior circulation syndrome (TACS)	39	4	60	4
Partial anterior circulation syndrome (PACS)	4	56	4	56
Lacunar syndrome (LACS)	2	62	2	62
Posterior circulation syndrome (POCS)	7	62	7	62

Table 2 NICE recommendations for urgent CT scanning[1]

NICE recommends the following as urgent indications for CT scanning (within 1 h)

- Indications for thrombolysis or early anticoagulation treatment
- Those on anticoagulant treatment
- Known bleeding tendency
- Depressed level of consciousness (GCS below 13)
- Unexplained progressive or fluctuating symptoms
- Papilloedema, neck stiffness, or fever
- Severe headache at onset of stroke symptoms
- All other patients should be imaged 'within a maximum of 24 h after onset of symptoms'

day, and excludes haemorrhage. Loss of sulci, insular ribbon, and grey–white matter differentiation may indicate the early phases of AIS. Other causative pathology such as haemorrhage, neoplasm, and abscess may also be revealed.

The role of contrast is primarily in searching for stroke mimics, e.g. tumour is contrast enhancing. Contrast is also given for CT angiography (CTA) and CT venography.

MRI: Diffusion-weighted magnetic resonance imaging (MRI) can provide enhanced detail and demonstrate early ischaemia (see Fig. 1). It is particularly useful if the diagnosis is uncertain or the territory is unclear. MR angiography (MRA), which can be done simultaneously, delineates vascular architecture and the presence of occlusive disease. Other imaging modalities that can be considered after expert consultation include CTA or digital subtraction angiography.

Carotid duplex scanning: Carotid duplex scanning is performed to allow identification of patients for early carotid intervention. All patients with an anterior circulation syndrome deemed candidates for carotid surgery should undergo duplex scanning. Ideally this should be performed early to allow carotid intervention within 1 week, with no benefit demonstrated from surgery after 12 weeks post event.

MR spectroscopy, transcranial Doppler ultrasonography (TCD), and single-photon emission computed tomography (SPECT) are available in limited units.

Other tests

Electrocardiography: atrial fibrillation is a major risk factor for AIS. It is also recognized that ischaemic-like ECG changes, QT prolongation or both may be seen in the majority of unselected patients with ischaemic stroke and intracerebral haemorrhage.

Elevated levels of cardiac troponin have also been reported. Myocardial injury in thrombotic (and also haemorrhagic) strokes may be neurally mediated via local release of norepinephrine from myocardial nerve terminals (the stunned myocardium). Prognostication using CVA-related elevations in troponin might be useful in predicting mortality.[3]

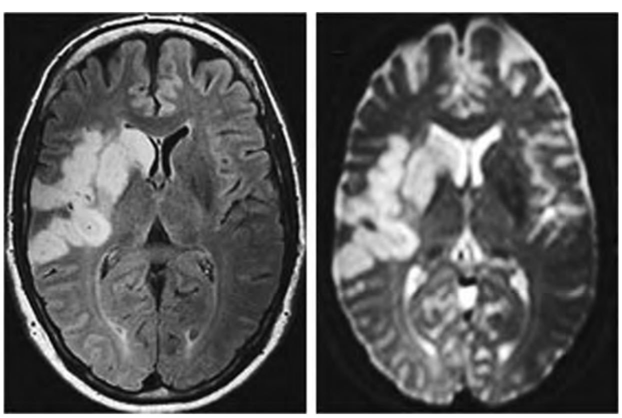

Fig 1 MRI scans obtained 2 days after the onset of ischaemic stroke in the territory of the right middle cerebral artery.

Transthoracic echocardiography should be considered in all young patients, if more than one territory is involved, if there is an audible murmur, or if the patient has an abnormal ECG.

Transoesophageal and bubble-contrast echocardiography or transcranial Doppler should be considered to exclude right to left intracardiac shunt if suspected.

Treatment

General treatments[1,2]

Aspirin and anti-platelet therapy: all patients with AIS, who have had primary cerebral haemorrhage excluded by imaging, should be given aspirin 300 mg orally (rectally/nasogastrically if dysphagic) as soon as possible and definitely within 24 h. AIS patients receiving thrombolysis should have aspirin withheld for 24 h after thrombolysis.

In line with recently updated RCP stroke guidelines, for those patients in sinus rhythm, clopidogrel should be substituted for secondary prevention when appropriate. The decision of when to commence clopidogrel should be taken on an individual patient basis. Patients with AIS secondary to arterial dissection should be discussed with a stroke specialist and treated with either anti-platelet or anticoagulation therapies.

Statin therapy: some controversy surrounds the immediate prescription of statins post AIS, as increased rates of haemorrhagic transformation have been reported, but clear evidence points to their long-term benefit in reducing future AIS risks. All patients should thus be considered for treatment with statin therapy after 48 h.

Multi-disciplinary treatments relevant to critical care:

- optimal positioning, passive movements and prevention of contractures
- avoidance of aspiration pneumonia, SALT assessments
- assessment of nutritional status and supplemental hydration and nutrition where appropriate, including nasogastric feeding in those unable to take adequate oral nutrition within 24 h
- hypotonic fluids should be avoided as they may worsen cerebral oedema
- all patients should be discharged to a dedicated stroke unit.

Thrombolysis

Patients presenting within 4.5 h of onset of AIS should be considered for thrombolysis with i.v. recombinant tissue plasminogen activator (alteplase-t-PA).[4]

The National Institute of Neurological Disorders and Stroke (NINDS) trial, published in 1995, provided evidence that r-TPA (alteplase) given to ischaemic stroke patients within 3 h of symptom onset improved functional outcomes at 3 months, with a number needed to treat of 8 for a good functional outcome. These results were duplicated in phase IV clinical observational studies of rtPA in routine clinical practice. There is a clear time-dependent benefit for t-PA with treatment within 90 min increasing the odds of a favourable outcome 2.8 fold. The third European Cooperative Acute Stroke Study (ECASS 3)[5] demonstrated that patients treated within the 180–270 min time window had a significantly increased chance of a better functional outcome at 3 months compared to those receiving placebo. The European licence for the use of rtPA has recently changed to reflect these findings. A pooled analysis of thrombolysis for AIS concluded that patients with AIS, benefit when thrombolysed up to 4·5 h.[6]

In May 2012 the largest randomized control trial to date of rtPA, the third international stroke trial, published its findings.[7] The trial again demonstrated the clear benefit of rtPA given within the first 3 h and suggested that there may be benefit in some patients with rtPA given up to 6 h post symptom onset. The individual patient analysis is still awaited and this will hopefully provide more information on this. Over 50% of the patients enrolled in this trial were aged over 80 yr and the results suggest that this group of patients benefit at least as much as those aged under 80 yr.

In select cases of intracranial arterial occlusion, for example internal carotid artery or proximal middle cerebral artery occlusion within 6 h of symptom onset, intra-arterial thrombolysis (IAT) and mechanical clot retrieval can be considered. This was traditionally performed under general anaesthesia as the airway is secure, head stable and access improved, although conscious sedation may allow a faster time to treatment and avoids the complications of general anaesthesia. Crucially, the choice of sedation or general anaesthesia for acute interventional procedures after AIS is dependent on the clinical status of the patient.No research difference has been shown between the two techniques, although patients having general anaesthesia during IAT appeared to have a higher chance of poor neurological outcome and a higher mortality compared with conscious sedation. This may now be the more desirable technique in appropriate patients. The relative merits of each technique of anaesthesia have been reviewed.[8,9] (Summarized in Table 3).

Anticoagulation for other conditions in AIS

The following are from the NICE guideline, however management decisions may vary on an individual patient basis.[1,2]

Atrial fibrillation and AIS: treat with aspirin 300 mg for initial 2 weeks before consideration of therapeutic anticoagulation.

Table 3 Pros and cons of general anaesthesia during acute ischaemic stroke interventions[7]

General tracheal anaesthesia	Conscious sedation
Pros	*Pros*
Limits mobility of patients	Monitoring for new neurological deficits
Decreased intra-operative procedure time	Clinical endpoint *vs* angiographic
Limits aspiration	More rapid intervention possible
Cons	*Cons*
Requires additional workforce	Increased contrast use
Delay time to start intervention	Overall procedure time prolonged
No clinical neurological monitoring	Movement induced vessel perforation
Anaesthesia risks in a non-fasted state	Emergent intubation may be required
Infrastructure and response time	Aspiration risk
Decrease in cerebral perfusion pressure	

Prosthetic heart valves and AIS: in patients who have high risk of haemorrhagic transformation (e.g. large MCA infarct) withhold anticoagulation for 1 week and substitute with 300 mg aspirin.

Symptomatic proximal deep vein thrombosis or pulmonary embolism and AIS: unless there are specific contraindications to anticoagulation, these patients should be therapeutically anticoagulated in preference to treatment with aspirin.

Systemic physiological management[1,2]

Supplemental oxygen therapy: stroke patients should not be given supplemental oxygen routinely, only if hypoxic with oxygen saturations below 95%.

Blood sugar control: management of an elevated blood glucose level after stroke should be similar to that of other acutely ill patients who have hyperglycaemia. NICE consensus recommends maintaining blood glucose between 4 and 11 mmol litre^{-1}, although overly aggressive treatment can result in fluid shifts and electrolyte abnormalities including hypoglycaemia detrimental to the brain. The GIST-UK study, although underpowered, could not demonstrate any mortality or functional advantage in maintaining blood glucose to a tight range of 4–7 mmol litre^{-1}.[10]

Blood pressure control: guidelines recommend treatment of hypertension in the context of AIS in the following circumstances:

- hypertensive encephalopathy, nephropathy, cardiac failure,
- myocardial infarction,
- aortic dissection,
- pre-eclampsia/eclampsia,
- intracerebral haemorrhage with systolic blood pressure >200 mm Hg.

Blood pressure should be controlled to ≤185/110 mm Hg in patients who may be appropriate for thrombolysis, and treatment given to patients who are not thrombolysis candidates whose blood pressure is >220 mm Hg systolic or >120 mm Hg diastolic on repeat measurements, or whose mean arterial pressure exceeds 130 mm Hg.[11]

It should be emphasized that there is uncertainty about when to treat blood pressure with guidelines reflecting consensus opinion. Approximately 50% of patients admitted with AIS are taking prescribed antihypertensive medication. No data exist as to whether it is beneficial or safe to stop or continue this treatment during the acute phase. The Efficacy of Nitric Oxide in Stoke (ENOS) trial is currently ongoing, designed to address two questions related to the management of blood pressure immediately post-stroke:

- the safety and efficacy of nitric oxide, given as transdermal glyceryl trinitrate,
- the safety and efficacy of stopping or continuing prior antihypertensive medication.

The rationale for treatment is to lower the risk of haemorrhagic transformation, although aggressive blood pressure reductions may adversely affect cerebral perfusion, especially in the penumbra, thus exacerbating ischaemic damage. There is no consensus on when to treat low blood pressure, but in a patient who is markedly hypotensive, it would seem prudent to stop any antihypertensive treatment and initiate fluid therapy where necessary.

Other specific therapies

Temperature control and cooling: it is recognized that up to a quarter of patients may be hyperthermic in the initial 6 h after AIS, with observational data suggesting an association between high body temperature and poor outcome. The use of therapeutic hypothermia in acute stroke offers potential for combination therapy with aspirin and rt-PA, by attenuating blood–brain barrier permeability and the endogenous inflammatory CNS response after AIS (e.g. attenuation of pro-inflammatory astrocytes and microglia). The fact that hypothermia also lowers metabolic and energy demands may also have implications for extending the window for thrombolysis.

A Cochrane database review[12] of cooling in AIS found no significant effect on reducing the risk of a poor outcome or death. The European Stroke Research Network for Hypothermia (EuroHYP) network is currently involved in research investigating the potential uses of hypothermia as a treatment for AIS.

Avoidance of hyperthermia would therefore appear prudent, although therapeutic hypothermia for AIS is not currently recommended outside of trial studies.

Prophylaxis of deep venous thromboembolism (DVT)

Graduated compression stockings (GCS): the CLOTS trial collaboration[13] found that there was no significant reduction in DVT incidence with thigh length GCS, but there was an increase in incidence of skin complications, such as ulcers and blisters. As a result, GCS are no longer recommended for DVT prophylaxis in AIS.

Intermittent pneumatic compression (IPC) devices: mechanical compression stockings such as 'Flowtrons' are routinely used on intensive care units. The CLOTS 3 trial is currently ongoing to establish the effectiveness of IPC in preventing post-stroke DVT.

Low molecular weight heparin (LMWH): although there is trial data supporting the routine use of prophylactic-dose LMWH in immobile patients with AIS,[14] this study did not include a control group and its generalizability continues to be debated. The UK expert consensus currently does not recommend the routine use of prophylactic LMWH in addition to full-dose aspirin, due to the risk of haemorrhagic transformation of ischaemic infarcts. Decisions regarding high-risk patients should be on an individual patient basis.

Hemicraniectomy

Malignant MCA infarction is a devastating form of ischaemic stroke, which accounts for between 1 and 10% of supratentorial infarction and which carries an 80% mortality. Decompressive hemicraniectomy is a potentially life-saving treatment for the condition, acting by normalizing intracranial pressure, restoring penumbral and adjacent vascular territory blood flow and preventing herniation.

The evidence for surgery comes predominantly from a pooled analysis of three European randomized control trials of 93 patients.[15] A favourable outcome was seen in 75% of those treated surgically, compared with 24% treated medically and there was also a significant difference in survival between the surgical and medical groups. The absolute risk reduction was 49%, which translates into a number needed to treat of two to avoid one fatality.

Patients included in the trials were aged 18–60 yr, and there is currently no evidence to support the use of decompressive hemicraniectomy in the elderly (Fig. 2).

Risk of anaesthesia and AIS[16,17]

After adjustment for identifiable risk factors, there is independent risk of incident AIS in the 30 days after surgery and anaesthesia. This extends for both high-risk (cardiac, vascular) and low-risk surgeries. It has also been shown that a previous neurological event (AIS, TIA) is an independent risk factor for perioperative AIS.

The timing of surgery and anaesthesia after AIS is not well studied and precise guidance is beyond the scope of this article. However, a publication within this journal has a proposed scheme (readers are directed to the reference for a thorough review):[17]

- *High cerebrovascular risk*: within 2 weeks of AIS, all elective surgery should be postponed, vital or emergency surgery will need appropriate anti-platelet cover in the context of the surgical haemorrhage risk category (seek expert guidance).
- *Intermediate cerebrovascular risk*: 6–24 weeks after an uncomplicated stroke, low surgical haemorrhagic risk elective surgery can proceed with aspirin therapy maintained, intermediate- and high-risk elective surgery should be postponed. It is likely prudent that only vital surgery is undertaken in the initial 6 weeks after a stroke.
- *Low cerebrovascular risk*: >6 months after a stroke (or 12 months if complications), all elective surgery can proceed with aspirin therapy maintained, except for high surgical

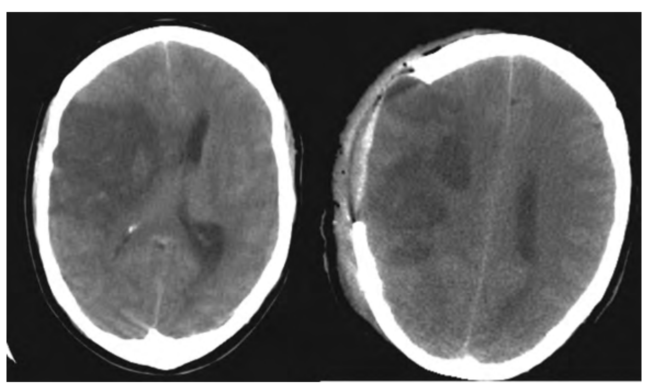

Fig 2 CT image pre- and post-craniectomy

haemorrhagic risk (e.g. intracranial neurosurgery) where aspirin should be withdrawn for a maximum of 7 days however in these cases the individual risk–benefit ratio must be evaluated and early post-operative reinstitution implemented.

- Some articles cite 3 months after a stroke as being a low-risk situation.

Implications for critical care[18,19]

Intensive care units are likely to have an increasing role in the management of AIS patients, therapeutic goals being avoidance of secondary brain injury, and facilitating new management strategies in patient care. Stratifying which patients with AIS need to be admitted to ICU is difficult and should be done in liaison with neuromedical teams, indications may include:[18]

- deteriorating neurological status and airway compromise
- seizures
- to facilitate therapeutic interventions
- brainstem infarcts, in particular related to the basilar artery
- large space occupying hemispheric infarcts with mass effect
- respiratory failure that may be related to aspiration pneumonia, depressed central respiratory drive, or neurogenic pulmonary oedema.

Mechanical ventilation should normally be initiated when Pa_{O_2} values decrease to <8–9.3 kPa or Pa_{CO_2} values exceed 6.6–8 kPa.[19]

Invasive monitoring of AIS patients requiring ICU care may include central venous and arterial catheterization for observation and control of blood pressure. Continuous cardiac monitoring is mandatory and may allow recognition of causative arrhythmias associated with AIS such as atrial fibrillation and secondary pathology such as ischaemic changes and dysrhythmias (e.g. right temporal lobe strokes are associated with ventricular tachycardia). Continuous electroencephalogram (EEG) monitoring is useful in determining seizure activity and can also detect cessation of blood flow to ischaemic areas of the brain seen after AIS. Increased intracranial pressure in patients with large hemispheric infarction may warrant the use of intracranial pressure monitoring, where decompressive craniectomy and ventriculostomy may prove life saving. Transcranial Doppler (TCD) ultrasonography is a non-invasive bedside device, which can immediately assess blood flow within the brain and thus potential evolving ischaemia seen within AIS. Single-photon emission computerized tomography (SPECT) and near infrared (NIR) spectroscopy are monitoring techniques that may be seen more within ICUs in the future.

Other routine critical care considerations such as physiotherapy exercises for limbs rendered weak or immobile secondary to stroke, prevention of pulmonary emboli, aspiration, ventilator-acquired pneumonia and skin breakdown, and nutritional support are also important. The use of appropriate levels of sedation requires careful consideration, with excessive or inappropriate usage affecting the clinicians' ability to monitor the patient with serial neurological examinations.

Optimizing cerebral blood flow, cerebral perfusion pressure, and metabolism, and also preventing brain oedema and elevations in intracranial pressure, are therapeutic goals well known in the care of neurological ICU patients. These include maintenance of adequate oxygenation to a brain in which supply is already compromised and avoidance of hypercapnia, which can cause cerebral arteriolar vasodilation of cerebral arterioles supplying healthy brain tissue, at the expense of maximally, dilated vessels supplying ischaemic areas.

Accurate assessment of the impact of ICU care on survival and functional outcome is needed, to help guide decision-making and evaluate resource consumption.

AIS patients requiring long-term ventilation will need consideration for tracheostomy, as the subsequent reduction in analgesics and sedatives will allow easier assessment of neurological status. The optimal timing of tracheostomy in patients with stroke is unknown and is currently subject to trial (the SETPOINT trial). Outcome data for patients needing mechanical ventilation have reported mortality rates between 46 and 92% with the need for MV and PEG being markers for poor long-term outcome.

Difficult ethical decisions relating to critical care admission and withdrawal of care should be made in full consultation with all specialities involved, the multi-disciplinary team and where appropriate the patient and next of kin.

This review has provided an overview of the recent developments within the management of AIS. Improved education, together with better organization of stroke services, is likely to improve the recovery from this potentially devastating condition.

Declaration of interest

None declared.

References

1. NICE Guideline. Diagnosis and initial management of acute stroke and transient ischaemic attack (TIA). July 2008
2. Intercollegiate Stroke Working Party. *National Clinical Guideline for Stroke*, 3rd edn. London: Royal College of Physicians, 2008
3. Chalela JA, Ezzeddine MA, Davis L *et al.* Myocardial injury in acute stroke: a troponin I study. *Neurocrit Care* 2004; **1**: 343–6
4. The ATLANTIS, ECASS, and NINDS (The National Institute of Neurological Disorders and Stroke) rt-PA Study Group Investigators. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet* 2004; **363**: 768–74
5. Hacke W, Kaste M, Bluhmki E, Brozman M *et al.* For the ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008; **359**: 1317–29
6. Lees KR, Bluhmki E, von Kummer R, Brott TG *et al.* Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet* 2010; **375**: 1695–703
7. Lindley R, Wardlaw J, Dennis M *et al.* The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. *Lancet* 2012; **379**: 2352–63

8. Abou-Chebl A, Lin R, Hussain MS *et al.* Conscious sedation versus general anaesthesia during endovascular therapy for acute anterior circulation stroke: preliminary results from a retrospective, multicenter study. *Stroke* 2010; **41**: 1175–9
9. Mcdonagh D, Olson DM, Kalia JS, Gupta R *et al.* Anesthesia and sedation practices among neurointerventionalists during acute ischemic stroke endovascular therapy. *Front Neurol* 2010; **1**: 118
10. Gray CS, Hildreth AJ, Sandercock PA *et al.* GIST Trialists Collaboration. Glucose–potassium–insulin infusions in the management of post-stroke hyperglycaemia: the UK Glucose Insulin in Stroke Trial (GIST-UK). *Lancet Neurol* 2007; **6**: 397–406
11. Adams HP, del Zoppo G, Alberts MJ *et al.* Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association. *Stroke* 2007; **38**: 1655–711
12. Den Hertog HM, van der Worp HB, Tseng MC, Dippel DWJ. Cooling therapy for acute stroke (Review). *Cochrane Database Syst Rev* 2009; CD001247
13. The CLOTS Trials Collaboration. Effectiveness of thigh-length graduated compression stockings to reduce the risk of deep vein thrombosis after stroke (CLOTS trial 1): a randomised controlled trial. *Lancet* 2009; **373**: 1958–65
14. Sherman DG, Albers GW, Bladin C, Fieschi C *et al.* The efficacy and safety of enoxaparin versus unfractionated heparin for the prevention of venous thromboembolism after acute ischaemic stroke (PREVAIL Study): an open-label randomised comparison. *Lancet* 2007; **369**: 1347–55
15. Vahedi K, Hofmeijer J, Juettler E *et al.* For the DECIMAL, DESTINY, and HAMLET investigators. Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomized controlled trials. *Lancet Neurol* 2007; **6**: 315–22
16. Wong G, Warner D, Schroeder D, Offord K *et al.* Risk of surgery and anaesthesia for ischaemic stroke. *Anaesthesiology* 2000; **92**: 425–32
17. Chassot PG, Delabays A, Spahn DR. Perioperative antiplatelet therapy: the case for continuing therapy in patients at risk of myocardial infarction. *Br J Anaesth* 2007; **99**: 316–28
18. Diedler J, Sykora M, Juttler E, Steiner T, Hacke W. Intensive care management of acute stroke: general management. *Int J Stroke* 2009; **4**: 365–78
19. Golestanian E, Jinn-Ing L, Smith MA. Long-term survival in older critically ill patients with acute ischaemic stroke. *Crit Care Med* 2009; **37**: 3107–13

Please see multiple choice questions 9–12.