

Management of acute ischaemic stroke: new guidelines from the American Stroke Association and European Stroke Initiative

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Background

Ischaemic stroke is an important cause of death and dependency in industrialised countries; it has a high incidence (affecting up to 0.2% of the population each year) and is commonly lethal or disabling. One in six patients die in the first month after ischaemic stroke, and half of survivors are permanently disabled despite best efforts to rehabilitate them and to prevent complications, recurrent stroke, and other serious vascular events. Optimisation of the early, and ongoing, management of patients with acute ischaemic stroke is pivotal to the reduction of both case fatality and long-term disability.

Recent developments

Guidelines for the early management of patients with ischaemic stroke have recently been published by the Stroke Council of the American Stroke Association (ASA; Adams and co-workers, *Stroke* 2003; **34**: 1056–83) and the European Stroke Initiative (EUSI; European Stroke Initiative Executive Committee and Writing Committee, *Cerebrovasc Dis* 2003; **16**: 311–38). Although transatlantic differences might create different interpretations, priorities, and views, the guidelines are remarkably similar, even regarding controversial issues. We believe this is not only because both groups have had the opportunity to discuss many of the controversial issues at international meetings, but also because both groups have endorsed the concept of evidence-based medicine and have based their recommendations on similar classifications of the levels of evidence for the effectiveness of interventions. This is a triumph for evidence-based medicine and a major step towards unification of acute stroke management worldwide.

Where next?

There are three main challenges in stroke management. To increase the body of reliable evidence from large randomised controlled trials (RCTs) of the safety, effectiveness, and cost of promising treatments (eg, thrombolysis, antithrombotic therapy, neuroprotection, and interventional recanalisation, alone and in combination) in a wide range of patients around the world. To facilitate the widespread development of stroke units, delivery of organised stroke care, and emergency transport of patients with stroke to appropriate stroke centres. And finally, to improve the uptake of effective therapies into clinical practice (eg, by widely disseminating the ASA and EUSI guidelines).

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In the recent evidence-based guidelines and recommendations for the management of stroke published by the American Stroke Association (ASA)¹ and the European Stroke Initiative (EUSI),² the ASA concentrates on

the early diagnosis and management of patients in the first 24–48 h of ischaemic stroke,¹ whereas the EUSI also addresses the various strategies of primary and secondary stroke prevention, rehabilitation, improvement of public awareness of the symptoms of stroke, and the need for urgent medical attention after a stroke.²

Diagnosis

The ASA superbly describes the clinical assessment of patients with suspected stroke and emphasises that the clinical history and examination are the cornerstones. The ASA and EUSI both agree that a CT brain scan is the most important diagnostic test to exclude non-vascular, structural, intracranial lesions as the cause of the focal neurological symptoms, to differentiate between brain ischaemia and haemorrhage, to ascertain the likely aetiology and prognosis, and to guide acute intervention. MRI can be substituted for CT but it is contraindicated in more patients (eg, those with metal implants, cardiac pacemakers, or claustrophobia), less widely available, more costly, and less reliable in identifying acute intracranial haemorrhage. Although MRI is more sensitive in the detection of brain infarction, the ASA and EUSI concur that further research is required to determine whether diffusion and perfusion MRI, and magnetic resonance spectroscopy, may be of additional help for the assessment of the risk to benefit ratio for early reperfusion therapy. Vascular imaging (ultrasound, CT angiography, and magnetic resonance angiography) offers additional information about vessels in the brain and neck.

Stroke-care delivery

Site

EUSI states that most patients with suspected stroke should not be managed at home, but should be transported without delay to a hospital, which has access to the required diagnostic tests 24 h/day and 7 days/week.¹ Once admitted, both guidelines recommend that patients should be managed in a stroke unit rather than a general medical ward (level I). This recommendation is based on evidence from a

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systematic review of RCTs. Compared with alternative services, organised inpatient care in a stroke unit reduces the odds of death or dependency at final follow-up by 22% (95% CI 11–32). This reduction means that organised stroke unit care will lead to about 50 (20–85) fewer dead or dependent people per 1000 treated.³ The latter estimate depends on the baseline risk of the individual patient.

Neither guidelines specify whether care in a stroke unit should be dedicated to stroke care only versus a mixed ward or to stroke patients of a certain severity, but both infer that monitoring in an intensive care setting is not necessary.

Process

Both the ASA and EUSI recommend that stroke care should be specialised, organised, and multidisciplinary (ie, provided by medical, nursing, physiotherapy, occupational therapy, speech therapy, and social work staff who are interested and trained in stroke care; level 1). The multidisciplinary stroke team should meet regularly to discuss patients' assessments, goals, progress, management, and discharge plans. The EUSI document discusses the variability of stroke care among different countries and centres, but neither guideline offers solutions to the wide disparities in access to and quality of care within each region.

General supportive care to maintain physiological homeostasis

Despite the absence of reliable evidence for the effectiveness of interventions aimed at the maintenance of physiological homeostasis, the ASA and EUSI guidelines are remarkably consistent in their support for this concept. Airway support and ventilatory assistance is recommended for patients with reduced consciousness or a compromised airway. Supplemental oxygen is recommended for patients with hypoxaemia (target O₂ saturation: EUSI \geq 92%; ASA \geq 95%). Antipyretic agents are indicated if the body temperature is high (high temperature defined as: EUSI \geq 37.5°C; ASA no temperature threshold stated), as is identification and treatment of the cause (eg, with antibiotics). Gradual lowering of high glucose concentrations in the blood is recommended (target glucose concentration: EUSI about 10 mmol/L; ASA <16.63 mmol/L) with normal saline and insulin titration. Low blood glucose concentrations should be rapidly corrected with intravenous dextrose bolus or infusion of 10–20% glucose, and hypotonic solutions (NaCl 0.45% or glucose 5%) should be avoided to minimise brain oedema and the probable detrimental effects of hyperglycaemia associated with glucose infusions (all level IV recommendations).

The management of high blood pressure in acute stroke is highly controversial (due to a lack of reliable [level 1] evidence from randomised controlled trials). However, both the ASA and EUSI are consistent in not recommending routine lowering of blood pressure unless it is repeatedly >200–220 mm Hg systolic or >120 mm Hg diastolic in a patient with ischaemic stroke, or >180/105 mm Hg in a patient with haemorrhagic stroke. In such cases, labetalol and sodium nitroprusside are suggested by both groups, as

well as avoidance of drugs such as sublingual nifedipine, which are rapidly absorbed and can cause precipitous reductions in blood pressure. The ASA also recommends nicardipine, whereas EUSI also recommends intravenous urapidil, nitroglycerin, and oral captopril. The ASA recommends a 10–15% reduction in blood pressure, whereas EUSI recommends target blood pressure of 180/100–105 mm Hg in patients with previous hypertension, and 160–180/90–100 mm Hg in patients without previous hypertension. Both guidelines recommend a target blood pressure of <180/110 mm Hg before thrombolysis is potentially indicated.

Specific treatment for acute ischaemic stroke

Reperfusion of ischaemic brain

The ASA and EUSI recommend intravenous alteplase (0.9 mg/kg, at most 90 mg), with 10% of the dose given as a bolus followed by an infusion lasting 60 min, for carefully selected patients who can be treated within 3 h of onset of ischaemic stroke. Thrombolysis with alteplase should be done by clinicians with expertise in stroke medicine, who have access to a suitable stroke service with facilities for immediate identification and management of haemorrhagic complications (level 1). Compared with placebo, thrombolysis within 3 h reduces the odds of death or dependency at final follow-up by 44% (95% CI 18–48); thus, alteplase would save 110 people (50–170) from death or dependency for every 1000 treated (depending on the patients' baseline risk).⁴

Both sets of guidelines agree that earlier treatment is more likely to be associated with a favourable outcome. However, they also discuss the potential, but as yet unproven, effectiveness of alteplase given beyond the 3 h time window. The EUSI concludes that, at present, intravenous alteplase should be given more than 3 h after ischaemic stroke only as part of a clinical trial.

The ASA and EUSI do not recommend intravenous alteplase when the time of onset of stroke cannot be ascertained reliably; this includes people whose strokes are recognised on waking (level IV). They also agree that no other intravenous thrombolytic drug has been proven to be a safe and effective alternative to alteplase, and that currently available data do not support the clinical use of either streptokinase or anecrod (a defibrinating enzyme) outside of clinical trials.

Neither the ASA nor the EUSI quantify the risks of bleeding associated with thrombolysis from a systematic review from all RCTs. Current evidence suggests that the treatment with alteplase increases, by three times, both the risk of symptomatic intracranial haemorrhage (10% with alteplase vs 3% with placebo; odds ratio [OR] 3.1, 95% CI 2.3–4.2, absolute excess 62 per 1000 patients treated) and of fatal intracranial haemorrhage within 7–10 days (4% with alteplase vs 1% placebo; OR 3.6, 2.3–5.7, absolute excess 25 per 1000 patients treated; level 1).⁴

The EUSI states that intra-arterial treatment of acute middle cerebral artery occlusion with prourokinase in a 6 h time window results in improved outcome (level II), but the ASA is more conservative. The ASA suggests that intra-

arterial thrombolysis is an option for treatment of selected patients with major ischaemic stroke due to occlusion of the middle cerebral artery less than 6 h from onset, with the caveat that these data are based on a trial of recombinant prourokinase, which is not available for clinical use, and that intra-arterial thrombolysis is not approved by the FDA (because it has not been shown to be effective and safe in at least two double-blind, placebo-controlled, randomised trials). Both ASA and EUSI agree that the evidence for intra-arterial thrombolysis of acute basilar artery occlusion is limited to small case series, and that this procedure should be done only as an experimental therapy in specialist stroke centres by experienced personnel according to protocol, and preferably as part of a multicentre clinical trial.

Protection of ischaemic brain cells

The ASA and EUSI agree that currently, no agent with putative neuroprotective effects can be recommended for the treatment of patients with acute ischaemic stroke (level I).

Augmentation of cerebral blood flow

Both ASA and EUSI concur that strategies to improve blood flow by changing the characteristics of the blood (eg, isovolaemic haemodilution) or by increasing cerebral perfusion pressure (eg, hypervolaemic haemodilution) have not been established as useful (level 1). The ASA warns that these therapies are associated with a risk of serious neurological and cardiovascular complications.

Prevention of early recurrent ischaemic stroke

Aspirin

The ASA and EUSI agree that the use of aspirin should be started within 48 h after ischaemic stroke (level I), unless thrombolytic therapy is planned, in which case aspirin should be withheld for 24 h. This recommendation is based on evidence that, compared with control, aspirin 160–300 mg/day (started within 48 h of stroke onset and continued for 10–28 days) reduced the odds of recurrent stroke during the treatment period by 13% (95% CI 3–21%) and of death or dependency at the end of follow-up by 5% (1–9%).⁵ This effect would result in 13 fewer dead or dependent people per 1000 treated with aspirin. The EUSI recommends aspirin 100–300 mg/day whereas the ASA makes no recommendation about the initial aspirin dose. The ASA states that no recommendation can be made about the immediate use of other antiplatelet drugs in acute ischaemic stroke.

Heparins

The ASA and EUSI do not recommend routine, urgent use of heparin, low-molecular weight heparin, or heparinoids after ischaemic stroke (outside of a clinical trial). The beneficial effects of these drugs of reduced risk of recurrent ischaemic stroke are offset completely by the hazards of increased risk of haemorrhagic transformation of the brain infarct (level 1).⁶ However, the EUSI recommends that “full-dose heparin may be used when there are selected indications such as cardiac sources with a high risk of re-embolism, arterial dissection, or high grade arterial stenosis

before surgery (level IV)”.² The ASA is more conservative, and urges further studies to determine if certain subgroups (large vessel atherothrombosis or patients perceived to be at high risk of recurrent embolism) may benefit from urgent anticoagulation. In addition, the ASA does not recommend urgent anticoagulation for patients with moderate-to-severe stroke because of a high risk of serious intracranial bleeding complications.¹

Revascularisation procedures

The ASA states that there are no definitive data about the effectiveness and safety of carotid endarterectomy, extracranial–intracranial arterial bypass, or endovascular treatments (eg, angioplasty, stent, clot removal, suction thrombectomy, and thrombolysis assisted by laser and power Doppler) for patients within the first few hours to days of acute ischaemic stroke. Therefore, these treatments are not recommended outside of a research setting. The EUSI does not discuss these.

Prevention of complications

Medical complications

Although not proven by randomised controlled trials, both the ASA and the EUSI state that early mobilisation is favoured to prevent numerous complications after stroke including aspiration pneumonia, venous thromboembolism, decubital ulcers (pressure sores), and contractures.

Infections

Both ASA and EUSI recommend that infections after stroke should be treated with appropriate antibiotics. The EUSI highlights that aspiration pneumonia cannot be prevented by nasogastric tube feeding (level IV).

Venous thromboembolism

The EUSI states that the incidence of venous thromboembolism may be reduced by early rehydration and mobilisation, and graded external compression stockings (level IV), and that low dose subcutaneous heparin or low molecular weight heparins should only be used in patients at high risk of venous thromboembolism (level II). In contrast, the ASA recommends subcutaneous anticoagulants to prevent venous thromboembolism for all immobilised patients, or the use of intermittent external graduated compression stockings or aspirin for patients who cannot receive anticoagulants.

Neurological complications

Brain oedema and high intracranial pressure

The ASA and EUSI agree in all components of of this section. They feel that corticosteroids have no place in the management of cerebral oedema and may cause increased intracranial pressure after ischaemic stroke (level 1). Osmotherapy and hyperventilation are recommended for patients whose condition is deteriorating secondary to high intracranial pressure, including those with herniation syndromes (level IV). External ventricular drainage or ventriculostomy can be used to treat increased intracranial pressure due to hydrocephalus (level III). Surgical

decompression and evacuation of large cerebellar infarctions that compress the brainstem and cause hydrocephalus is justified (level III). And surgical decompression with evacuation of a large hemispheric infarction can be a life-saving measure but needs further investigation. The ASA pessimistically states that most survivors have severe residual neurological deficits (level III) whereas the EUSI optimistically emphasises that survivors may have residual neurological deficit that allows an independent life (level III).

Seizures

The EUSI and ASA agree that prophylactic use of anticonvulsants in patients with recent stroke who have not had seizures is not recommended (level IV), whereas recurrent seizures should be treated as with any other acute neurological disorder.

Conclusion

The new guidelines for the management of acute ischaemic stroke by the ASA and EUSI are evidence-based, comprehensive, up-to-date, and consistent overall.

Both the ASA and EUSI emphasise that stroke is a medical (and in some cases a surgical) emergency, and so time is of the essence in acute stroke care. Accurate diagnosis, early reperfusion where appropriate, implementation of effective therapies to minimise recurrent stroke and complications, and maximised rehabilitation will improve patient outcome. The EUSI also highlights the effectiveness of long-term strategies of primary and secondary stroke prevention, rehabilitation, and the need for improved public awareness of the symptoms of stroke and importance of seeking urgent medical attention after stroke. Minor disagreements and inconsistencies between the ASA and EUSI guidelines about acute treatment of particular patients with intra-arterial thrombolysis, heparin, and craniectomy; secondary prevention with clopidogrel as a substitute for ticlopidine; and heparin prophylaxis of venous thromboembolism reflect different interpretations of unreliable (level III and level IV) evidence. The American document distances itself from the weaker data whereas the European document encompasses them.

Practising clinicians and their patients will benefit from the clear recommendations for proven interventions, and

Search strategy and selection criteria

Data for this review were identified by searches of MEDLINE and the Cochrane Library with the search terms “guidelines”, “ischaemic stroke”, and “early management”, and references from relevant articles. Articles published in 2003 and in English were considered. The guidelines for the early management of patients with ischaemic stroke recently published by the Stroke Council of the American Stroke Association and the European Stroke Initiative were reviewed, and we have attempted to summarise them here.

researchers will benefit from the identification of clinically important questions that remain to be resolved.

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Authors' contributions

GJH reviewed and summarised the relevant data and wrote the first and final drafts of the review. CJMK reviewed and summarised the relevant data and wrote the second draft.

Conflict of interest

GJH is the Australian national coordinator of the Third International Stroke Trial (IST-3) and a member of the Writing Committee of the the Stroke Unit Trialists' Collaboration.

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