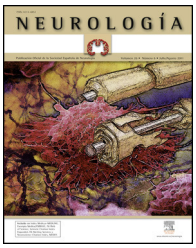
Neurología. 2014;29(2):102—122

NEUROLOGÍA

www.elsevier.es/neurologia



REVIEW

Guidelines for the treatment of acute ischaemic stroke☆

M. Alonso de Leciñana*, J.A. Egido, I. Casado, M. Ribó, A. Dávalos, J. Masjuan, J.L. Caniego, E. Martínez Vila, E. Díez Tejedor (Coordinator), representing the *ad hoc* committee of the SEN Study Group for Cerebrovascular Diseases: B. Fuentes (Secretaría), J. Álvarez-Sabin, J. Arenillas, S. Calleja, M. Castellanos, J. Castillo, F. Díaz-Otero, J.C. López-Fernández, M. Freijo, J. Gállego, A. García-Pastor, A. Gil-Núñez, F. Gilo, P. Irimia, A. Lago, J. Maestre, J. Martí-Fábregas, P. Martínez-Sánchez, C. Molina, A. Morales, F. Nombela, F. Purroy, M. Rodríguez-Yañez, J. Roquer, F. Rubio, T. Segura, J. Serena, P. Simal, J. Tejada, J. Vivancos[1]

Received 5 September 2011; accepted 11 September 2011
Available online 12 February 2014

KEYWORDS
Cerebral infarct;
Ischaemic stroke;
Thrombolysis;
Brain protection;
Stroke units;
Cerebral venous thrombosis

Abstract
Introduction: Update of Acute Ischaemic Stroke Treatment Guidelines of the Spanish Neurological Society based on a critical review of the literature. Recommendations are made based on levels of evidence from published data and studies.
Development: Organised systems of care should be implemented to ensure access to the optimal management of all acute stroke patients in stroke units. Standard of care should include treatment of blood pressure (should only be treated if values are over 185/105 mmHg), treatment of hyperglycaemia over 155 mg/dl, and treatment of body temperature with antipyretic drugs if it rises above 37.5 °C. Neurological and systemic complications must be prevented and promptly treated. Decompressive hemicraniectomy should be considered in cases of malignant cerebral oedema. Intravenous thrombolysis with rtPA should be administered within 4.5 hours from symptom onset, except when there are contraindications. Intra-arterial pharmacological thrombolysis can be considered within 6 hours, and mechanical thrombectomy within 8 hours from onset, for anterior circulation strokes, while a wider window of opportunity up to 12—24 hours is feasible for posterior strokes. There is not enough evidence to recommend routine use of the so-called neuroprotective drugs. Anticoagulation should be administered to patients with cerebral vein thrombosis. Rehabilitation should be started as early as possible.
Conclusion: Treatment of acute ischaemic stroke includes management of patients in stroke units. Systemic thrombolysis should be considered within 4.5 hours from symptom onset.

☆ Please cite this article as: Alonso de Leciñana M, Egido JA, Casado I, Ribó M, Dávalos A, Masjuan J, et al. Guía para el tratamiento del infarto cerebral agudo. Neurología. 2014;29:102—122.

* Corresponding author.
E-mail address: malonsoc.hrc@salud.madrid.org (M. Alonso de Leciñana).
[1] The affiliations of the authors and composition of the committee are listed in the addendum.

Intra-arterial approaches with a wider window of opportunity can be an option in certain cases. Protective and restorative therapies are being investigated.

PALABRAS CLAVE
Infarto cerebral;
Ictus isquémico;
Trombólisis;
Cerebroprotección;
Unidades de ictus;
Trombosis venosa cerebral

Guía para el tratamiento del infarto cerebral agudo

Resumen
Introducción: Actualización de la guía para el tratamiento del infarto cerebral agudo de la Sociedad Española de Neurología basada en la revisión y análisis de la bibliografía existente sobre el tema. Se establecen recomendaciones en base al nivel de evidencia que ofrecen los estudios revisados.
Desarrollo: Los sistemas de asistencia urgente extrahospitalaria se organizarán para asegurar la atención especializada de los pacientes y el ingreso en unidades de ictus (UI). Deben aplicarse cuidados generales para mantener la homeostasis (tratar la tensión arterial sistólica > 185 mmHg o diastólica > 105 mmHg, evitar hiperglucemia > 155 mg/dl y controlar la temperatura, tratando con antitérmicos cifras > 37,5 °C), y prevenir y tratar las complicaciones. La craniectomía descompresiva debe ser considerada en casos seleccionados de oedema cerebral maligno. La trombólisis intravenosa con rtPA se administrará en las primeras 4,5 horas en pacientes sin contraindicación. La trombólisis intraarterial farmacológica puede indicarse en las primeras 6 horas de evolución y la trombectomía mecánica hasta las 8 horas. En el territorio posterior la ventana puede ampliarse hasta 12—24 horas. No hay evidencias para recomendar el uso rutinario de los fármacos denominados neuroprotectores. Se recomienda la anticoagulación en pacientes con trombosis de senos venosos. Se aconseja el inicio precoz de rehabilitación.
Conclusiones: El tratamiento del infarto cerebral se basa en la atención especializada en UI, la aplicación urgente de cuidados generales y el tratamiento trombolítico intravenoso en las primeras 4,5 horas. La recanalización intraarterial farmacológica o mecánica pueden ser útiles en casos seleccionados. Terapias de protección y reparación cerebral están en desarrollo.

Since the publication of the most recent recommendations by the SEN Study Group for Cerebrovascular Diseases (GEECV/SEN),[1] there have been substantial improvements in some aspects of acute management of patients with cerebral ischaemia. This article provides updated recommendations on the care framework, general care for patients with acute-phase stroke, and specific treatment for ischaemia or for cerebral venous sinus thrombosis. Grades of recommendation and the scientific evidence supporting them are classified according to Centre for Evidence-Based Medicine (CEBM) criteria (Table 1).[2]

Care frameworks, 'code stroke', and stroke units

Stroke is a neurological emergency because the injury mechanisms following cerebral ischaemia or haemorrhage progress very quickly and treatments may only be effective during a short period of time. Highly effective and specific treatments are available, but their risk/benefit margin is narrow. With this in mind, organisational frameworks must be optimised and hospitals must be equipped and prepared to care for stroke patients.

The Helsingborg Declaration establishes the goal that all stroke patients will have easy access to diagnostic techniques (Table 2), as well as to treatments with demonstrated efficacy during the acute phase of the disease, referring specifically to access to neurological care and techniques used in stroke units (SU).[3,4] Given that these resources are expensive and it is not possible to provide them in all hospitals within a public health system with limited means, we must organise our care systems in such a way that all patients will have access, according to the characteristics of each health district.[5] This situation, plus the fact that most available treatments have a narrow therapeutic window, requires coordination between various levels of care to guarantee a minimum response time that will allow the patient to be evaluated and treated rapidly, in a hospital and by neurology specialists. To this end, implementing 'code stroke', the protocol for coordinated action by non-hospital emergency services and the hospitals that will care for the patient, has been a useful initiative. Pre-hospital 'code stroke' is the procedure that includes implementation of protocols developed by consensus, recognition of the emergency situation, and organisation of transport to suitable hospitals (those with an on-call neurologist, SU, and ability to provide specific treatments such as thrombolysis) after those hospitals have been alerted.[6—8] Pre-hospital 'code stroke' has been proved to decrease both care and treatment delays. Hospital emergency services should also organise care for these patients in order to reduce delays as much as possible. Action protocols created for this purpose are known as in-hospital code stroke, and they are also very effective (level of evidence 2a).[9—12]

Telemedicine systems that enable live communication between stroke centres of reference and hospitals lacking on-call neurologists may be useful as links to specialised resources where geographical barriers prevent or delay direct access. These systems help increase the number of

Table 1 Levels of evidence and grades of recommendation.

Level of evidence	Type of study on which classification is based	Grades of recommendation			
1a	Systematic review of randomised clinical trials (with homogeneity)	A	B (extrapolations from level 1 studies)		D (inconclusive studies)
1b	Randomised clinical trial with narrow confidence interval	A	B (extrapolations from level 1 studies)		D (inconclusive studies)
2a	Systematic review of cohort studies (with homogeneity)		B	C (extrapolation)	D (inconclusive studies)
2b	Individual cohort study (including low-quality randomised clinical trials, e.g. those with a follow-up level below 80%)		B	C (extrapolation)	D (inconclusive studies)
3a	Systematic reviews of case-control studies (with homogeneity)		B	C (extrapolation)	D (inconclusive studies)
3b	Case-control studies		B	C (extrapolation)	D (inconclusive studies)
4	Case series, cohort studies, or low-quality case-control studies			C	D (inconclusive studies)
5	Expert opinion based on physiology/pathophysiology or without explicit critical appraisal.				D

Source: Adapted from the Centre for Evidence Based Medicine (CEBM).[2]
Grade A recommendation: supported by level 1 studies.
Grade B recommendation: supported by level 2 or 3 studies (or extrapolation from level 1 studies).
Grade C recommendation: supported by level 4 studies (or extrapolation from level 2—3 studies).
Grade D recommendation: supported by level 5 studies only or inconclusive studies of any level.

patients evaluated by neurology specialists and the number of specific treatments administered, thereby reducing treatment delays (level of evidence 2a).[13]

Most stroke patients require hospitalisation. Possible exceptions include patients with a prior diagnosis of dementia or terminal illness and those not wishing to be hospitalised, provided that these cases will receive appropriate care outside the hospital.[14]

Stroke patients should be monitored in stroke units; studies with a 1A level of evidence show that SU care is linked to better outcomes due to reduced morbidity and mortality and a decreased probability of complications and/or dependence with an acceptable cost-efficiency ratio.[15—19] These benefits are the result of non-invasive neurological monitoring and the use of general care protocols intended to maintain homeostasis, in addition to proper application of specific treatments.[20—22] Care in SUs is linked to better care quality indicators (mean hospital stay, readmission, mortality, and need for institutionalisation) and it also significantly reduces monetary costs in stroke care.[19,23] SUs are structurally delimited divisions that are functionally dependent on neurology departments and provide specialised care to stroke patients. They are coordinated and staffed by neurology specialists with support from other related medical specialties (cardiology, vascular surgery, neuroradiology, neurosurgery, rehabilitation, emergency medicine, etc.), from physiotherapists who provide rapid treatment, and from social workers. They are equipped to provide non-invasive continuous monitoring and have trained nursing staff with a recommended nurse-to-patient ratio of at least 1:6. Their personnel and diagnostic services are available 24 hours a day, and their protocols and clinical channels for patient management are based on scientific evidence. The number of beds in the SU must be planned according to the needs and the size of the population served by the hospital. Stroke care plans recommend one monitored SU bed per 100 000 inhabitants.[24,25]

Admission criteria are as follows: patients with acute-phase stroke (<48 hours from onset), mild to moderate neurological deficit, and transient ischaemic attack. No age limits were established. Exclusion criteria are irreversible brain damage, prior dependent status or diagnosis of dementia, concurrent severe or terminal illness, and acute head trauma.

Recommendations

1. Recommendations call for admission to an acute SU with the necessary equipment (level of evidence 1a; grade A recommendation).
2. Emergency, in-hospital care is recommended for all patients with acute stroke (level of evidence 3a; grade B recommendation).
3. Reducing time to provide neurological care to a minimum and establishing specific pre-hospital care coordination systems are also recommended (level of evidence 2a; grade B recommendation).
4. Telemedicine systems with live, remote supervision by an expert neurologist may be useful to evaluate the patient and the specific treatment decision if in situ care is not available (level of evidence 1b; grade A recommendation).

Table 2 Thrombolytic treatment with rtPA.

Inclusion criteria

Patients with acute ischaemic stroke at less than 4.5 hours after onset and none of the following exclusion criteria.

Exclusion criteria

1. Intracranial haemorrhage in CT scan.
2. Elapsed time since onset > 4.5 hours or time of onset unknown.
3. Symptoms less pronounced or evolving favourably after starting rtPA infusion.
4. Severe stroke according to clinical assessment (NIHSS > 25) or neuroimaging criteria.
5. Symptoms suggesting subarachnoid haemorrhage although CT findings appear normal
6. Treatment with heparin in the preceding 48 hours and high aPTT level, or LMWH at anticoagulant doses in the preceding 12 hours.
7. Stroke in the preceding 3 months.
8. Platelet count below 10 000
9. Untreated glycaemic level below 50 mg/dL or above 400 mg/dL
10. Systolic blood pressure > 185 mmHg, diastolic blood pressure > 105 mmHg, or when aggressive means are required to bring blood pressure below these thresholds.
11. Known bleeding diathesis
12. Treatment with oral anticoagulants. Treatment with rtPA may be considered if INR $\leq$ 1.7.
13. Recent or manifest severe bleeding
14. History of intracranial haemorrhage.
15. History of SAH due to ruptured aneurysm.
16. History of central nervous system lesion (aneurysms, neoplasia, intracranial or spinal surgery).
17. Haemorrhagic retinopathy (ex. diabetic retinopathy).
18. History of cardiac massage, childbirth, or punctured inaccessible blood vessel in the preceding 10 days.
19. Bacterial endocarditis, pericarditis.
20. Acute pancreatitis.
21. Documented ulcerative gastrointestinal disease in the 3 preceding months. Oesophageal varices. Known intestinal vascular malformations.
22. Neoplasia with an increased risk of haemorrhage.
23. Severe liver disease (liver failure, cirrhosis, portal hypertension, active hepatitis).
24. Major surgery or significant trauma in the 3 preceding months

Regimen for administering rtPA

— Administer 0.9 mg/kg with 90 mg as the maximum dose; 10% of the total dose is delivered as a bolus over one minute and the rest of the dose will be infused continually over one hour.

Recommendations for general management and concomitant treatments

— Heparin and oral anticoagulants should not be administered in the 24 hours following rtPA treatment as they may increase risk of cerebral haemorrhage.
— Patients should be monitored, preferably in a stroke unit.
— A neurological examination should be performed every 15 minutes during the infusion, at the 2-hour mark, at the 24-hour mark, and any time the patient's condition deteriorates.
— Infusion should be continuous if there are clinical signs of bleeding (intense headache, vomiting, decreased level of consciousness, increased disability). In this case, an emergency CT will be performed.
— Avoid or delay placement of urinary catheters, nasogastric tubes, and arterial lines as much as possible.
— In cases of overdose, fibrinogen and other coagulation factors are often depleted. Waiting for normal physiological regeneration of these factors is usually sufficient. If haemorrhage occurs, follow the recommendations specific to the case.
— If there is an anaphylactic reaction, suspend the infusion and treat as appropriate.
— Blood pressure is to be checked every 15 minutes during the infusion and the first hour thereafter; every 30 minutes in the following 6 hours; and every hour until reaching the 24-hour mark. Blood pressure should be checked more frequently if it exceeds 180/105.

Blood pressure monitoring

— Blood pressure should be below 185/105 before the infusion is started.
— If blood pressure exceeds 185/105 in 2 measurements taken 5—10 minutes apart, treat according to current recommendations (see text). If these measures do not decrease the reading, the patient should not undergo thrombolysis. If blood pressure rises and cannot be lowered after treatment has been started, the infusion should be discontinued.

Managing haemorrhage after thrombolysis

— Cerebral haemorrhage should be suspected when the patient experiences neurological impairment, intense headache, vomiting, or a blood pressure spike.
— Systemic haemorrhage may be visible or occult (haemodynamic changes).

Table 2 (*Continued*)

- Discontinue rtPA infusion
- Perform emergency cranial CT (for cerebral haemorrhage).
- Measure coagulation times, fibrinogen, and platelets; run cross-match.
- Administer Haemocomplementan P® to replace fibrinogen: (1—2 vials, 1 g). The maximum dose is 2—3 g daily.
- Cryoprecipitates with a high platelet and factor VIII content, fresh plasma, and fresh blood are not recommended, since only fibrinogen will be depleted rather than the other factors listed above.
- Antifibrinolytic agents (tranexamic acid: amchafibrin®) may elicit thrombotic phenomena.

LMWH: low molecular weight heparin; SAH: subarachnoid haemorrhage; INR: international normalised ratio; NIHSS: National Institute of Health Stroke Scale; rtPA: recombinant tissue plasminogen activator; BP: blood pressure; CT: computed tomography; aPTT: activated partial thromboplastin time.

General care and non-pharmacological brain protection

Non-pharmacological brain protection refers to maintaining vital signs within normal limits (blood pressure, blood sugar, blood gas values, and body temperature), and preventing and detecting complications in their early stages. These measures significantly improve mortality and morbidity rates over the medium term, which is why a patient's vital signs and neurological status must be monitored in the first 48 hours after stroke, or until the patient is in stable condition.[21]

Maintaining proper respiratory function is a priority for the general management of these patients. In most cases, placing patients in a semi-seated position is sufficient. However, when respiratory function is compromised, patients will need orotracheal intubation and mechanical ventilation. Hypoxia due to partial airway obstruction, pneumonia, or hypoventilation may increase the area of the lesion and indicate a poorer prognosis.[26] Data indicate that administering supplementary low-flow oxygen to stroke patients reduces the rate of nocturnal desaturation (a common occurrence in these patients), and could therefore lead to better outcomes.[27] If readings show hypoxia (<95% oxygen saturation [SaO_2], the patient will require oxygen therapy (evidence level 2b).[10]

Blood pressure management

Arterial hypertension is very frequent during the acute phase of stroke. In many cases, it decreases spontaneously within a few days of stroke onset. During the acute phase of stroke, antihypertensive drugs should be used with caution. Since the mechanisms regulating cerebral circulation in the ischaemic area will be damaged, a decrease in perfusion pressure could compromise regional blood flow in the penumbra, thereby exacerbating ischaemia and worsening the patient's neurological state.[28] Numerous studies indicate that the relationship between mortality/functional prognosis after stroke and systolic/diastolic blood pressure follows a U-shaped curve. As such, the probability of death or dependency is higher for either low or high blood pressure values during the acute phase; the most favourable figures are 110—180/70—105 (evidence level 2a).[29—32] For this reason, treating high blood pressure is only recommended if systolic pressure is over 185 or diastolic pressure exceeds 105.

Data show that providing monitored treatment for hypertension during the acute phase of stroke is safe.[33—36] However, only one study shows that it is beneficial,[35] while others show no decrease in vascular events or any effects of treatment that would improve outcomes.[36] One study suggests treatment may be detrimental.[37]

When possible, doctors should administer oral drugs with little effect on regional cerebral blood flow, such as angiotensin receptor blockers, angiotensin convertase enzyme inhibitors, or beta-blockers.[35] Drugs eliciting rapid, intense decreases in arterial pressure, such as calcium channel blockers or diazoxide, are to be avoided. If drugs must be administered intravenously, their effect should be predictable and easily reversible, as in the cases of labetalol, urapidil, or nitroprusside. Drugs must be administered under strict surveillance to prevent sudden drop or any decreases of more than 20%.[1,32]

Certain exceptional situations that alter blood pressure levels call for treatment, such as co-presence of myocardial ischaemia, heart failure, aortic dissection, or hypertensive encephalopathy.

Once the acute phase is over, antihypertensive treatment should be started as a secondary prevention strategy, in accordance with specific guidelines.

Hypotension is uncommon following a stroke. It may be caused by a decrease in volume or failure to pump blood, and if the condition is present, doctors should rule out such complications as myocardial infarction, aortic dissection, pulmonary embolism, or digestive tract haemorrhage. In addition to treating the cause, hypotension should be corrected using volume expander drugs, and occasionally, vasodepressors (dopamine).

Hyperthermia is associated with poorer prognosis in cerebral infarct such that at temperatures exceeding 37.5°C, there is an increased probability of disease progression and death (level of evidence 2a).[38,39] Some studies show that treatment with antipyretic drugs improves outcomes in patients with high temperatures, but that these drugs are futile when used routinely in patients with normal temperatures (level of evidence 1b).[40] When a patient presents fever, doctors should investigate and treat the cause. Antipyretics (paracetamol or metamizole, as well as physical cooling means if necessary) are recommended if axillary temperature is higher than 37.5°C. Experimental data show that hypothermia reduces the size of the infarct. Clinical studies show that it is possible to induce hypothermia with physical or pharmacological means, but at this time, no data point to the utility of hypothermia as a technique for

improving functional outcomes or reducing mortality. In fact, hypothermia is associated with a greater risk of developing infectious complications, especially pneumonia.[41] However, there are initiatives promoting further studies of the utility of hypothermia under optimal clinical conditions for this treatment.[42,43]

Glycaemic control

Hyperglycaemia in the acute phase of stroke, as well as persistent hyperglycaemia > 155 in the first 48 hours after stroke onset, are linked to poorer functional outcomes and increased mortality (level of evidence 2b).[44–47] Hyperglycaemia is associated with infarct progression,[45] decreases the effectiveness of thrombolysis, and increases risk of haemorrhage following thrombolysis (level of evidence 2b).[48,49] Insulin treatment corrects hyperglycaemia in acute stroke, but this intervention has not been shown to provide better outcomes (level of evidence 1b).[50,51] The available data recommend maintaining glycaemia below 155 mg/dL and avoiding glucose solutions in the first 24 to 48 hours, except in diabetic patients who are more likely to experience hypoglycaemia, especially those who had previously been treated with oral antidiabetic agents.[46,47] However, hypoglycaemia should be treated by administering glucose. This condition may elicit focal conditions that resemble stroke or exacerbate existing symptoms; on the other hand, some stroke patients will not show symptoms of hypoglycaemia. For these reasons, we recommend monitoring glycaemia in all patients over at least 6 hours during the acute phase of stroke, or more frequently in cases in which glycaemia does not remain within the normal limits.

Hydration and nutritional balance

Undernutrition after a stroke promotes complications.[52–54] Patients may experience serious nutritional difficulties due to dysphagia or low level of consciousness. Enteral nutrition through a nasogastric tube is required if these conditions persist more than 48—72 hours.[54] Patients' ability to swallow should be examined daily to limit the risk of aspiration. Since dysphagia for liquids is more common, liquids should be avoided in early stages until after verifying that the patient can swallow normally. If the patient experiences dysphagia for liquids, dehydration can be prevented by providing liquids with thickeners or gelatine. Avoiding prolonged fasting reduces mortality and complication rates, but the effect on functional outcomes is unclear (level of evidence 1b).[54]

Physiotherapy in the acute phase

Early mobilisation reduces the incidence of other complications: shoulder pain, pressure ulcers, muscle spasms, pressure paralysis, etc. Published studies and meta-analyses indicate that physiotherapy and rehabilitation are effective for functional recovery over the medium term, and that therapy is more effective when started in early stages and focusing specifically on rehabilitation for concrete tasks (level of evidence 1a).[55–57] Although passive physiotherapy should be initiated early on, active rehabilitation should be postponed until the patient is in stable condition and not at risk for haemodynamic destabilisation.

Certain substances may delay recovery after a stroke due to their potential depressant effect on the central nervous system, especially substances with GABA agonists. As a result, they should be avoided as much as possible during the acute phase of stroke. These substances include neuroleptics, benzodiazepines and other anxiolytics, barbiturates, phenytoin and other anticonvulsants, and antispasmodic drugs. If these drugs are necessary, they should be administered with caution (level of evidence 3a).[58] On the other hand, early use of serotonin reuptake inhibitor-type antidepressants (fluoxetine, citalopram) in indicated cases has been observed to improve mood disorders and promote functional recovery (level of evidence 1a).[59–61]

Recommendations

1. Administering oxygen to patients with hypoxia (SaO_2 < 95%) is recommended, as is providing intubation and ventilation support to patients with compromised airway (level of evidence 2b; grade B recommendation).
2. Antihypertensive drugs should be used cautiously during the acute phase of stroke. Hypertension should be treated if systolic arterial pressure readings exceed 185 mmHg, or if diastolic readings exceed 105 mmHg (level of evidence 2a, grade B recommendation).
3. Hyperthermia exceeding 37.5°C is to be avoided. Among the drugs that have been studied, paracetamol has been shown to safely and effectively reduce body temperature (level of evidence 1b; grade A recommendation).
4. Avoid administration of glucose except to treat hypoglycaemia.
5. Glycaemia levels > 155 mg/dL should be prevented (level of evidence 2a; grade B recommendation).
6. Patients should be checked for dysphagia in order to prevent pulmonary aspiration. Doctors must prevent undernutrition and determine whether enteral nutrition with a nasogastric tube will be necessary during the first few days (level of evidence 1a; grade A recommendation).
7. Early use of passive mobilisation exercises is recommended (evidence level 1a; grade A recommendation).
8. Drugs that may have a detrimental effect on functional recovery should be avoided (level of evidence 3a; grade B recommendation).

Prevention and treatment of neurological complications decompressive craniectomy

The most frequent neurological complications are oedema and intracranial hypertension, epileptic seizures, and haemorrhagic conversion of a cerebral infarct.

Cerebral oedema after ischaemic stroke, with intracranial hypertension, may lead to cerebral herniation. This tends to be the cause of death within the first week after a large hemispheric infarct, especially in young patients

or cases of cerebellar infarct occurring with compression of the fourth ventricle and aqueduct of Sylvius and potential secondary hydrocephalus.[62] The term 'malignant middle cerebral artery infarction' (MMCAI) was coined to designate slowly evolving infarcts in this territory that are caused by either occlusion of the main trunk of the middle cerebral artery (MCA) or of the distal portion of the intracranial internal carotid artery (ICA).[63] The entity is characterised by clinical signs of total anterior circulation infarct with a decreased level of consciousness and radiological findings of ischaemia affecting more than 50% of the MCA territory. Following that, frank oedema appears with a more or less pronounced mass effect and midline shift; this is generally related to the decrease in consciousness. The mortality rate of MMCAI is 80%, even with aggressive medical treatment (intubation and anti-inflammatory drugs).[64] Clinical and radiological data let us predict this poor prognosis, which is helpful for selecting patients who may benefit from aggressive treatment. Careful monitoring is therefore the key to detecting decreased consciousness in early stages and providing treatment before damage becomes irreversible.

Treatment is initially preventive, and it consists of such general strategies as restricting fluids moderately and avoiding hypo-osmolar solutions (such as 5% glucose), and treating associated illnesses that could worsen oedema (hypoxia, hypercapnia, hyperthermia, arterial hypertension, urinary retention, etc. Other strategies include elevating the head of the bed 30° to improve venous return and decrease intracranial pressure (ICP) (level of evidence 3b).[65]

High doses of steroids should not be used as they neither lessen mortality nor decrease sequelae, but rather promote infection and complicate glycaemic control (level of evidence 1a).[66–68]

Osmotic agents (mannitol 20% or glycerol 10%) may decrease ICP, but their effect is temporary and they have not been proved effective for reducing mortality or sequelae. Routine use of osmotic agents is not recommended in cases of cerebral oedema in acute stroke (level of evidence 1a).[69–71] In the same way, hyperventilating an intubated patient to decrease the partial pressure of arterial carbon dioxide ($PaCO_2$) elicits a drop in intracranial pressure. However, since its effect is brief, it is used as an adjuvant technique prior to decompressive craniectomy.

Decompressive craniectomy in MMCAI has been shown to decrease mortality and, in some cases, sequelae as well. This is true when the technique is performed early (within 48 hours of symptom onset), in younger patients (≤60 years) and when clinical data do not indicate herniation or concomitant conditions that could increase the probability of complications such as haemodynamic instability, risk of haemorrhage, severe comorbidity, etc. (evidence level 1a) (Table 3).[72–76] Craniectomy must be extensive (at least 12 cm) with a dural aperture. Placing an ICP sensor has not been shown to be useful (level of evidence 2b).[77]

In cases of large cerebellar infarcts producing obstructive hydrocephalus or affecting the brainstem, suboccipital craniectomy[78] is an effective treatment for both hydrocephalus and brainstem compression (level of evidence 3a). This treatment is preferred to ventricular catheter placement, which may elicit upward transtentorial herniation of the oedematous cerebellum. Isolated ventricular drainage is therefore not recommended in these cases.[10] Time and age criteria are not as restrictive as in cases of hemicraniectomy in MMCAI.

Epileptic seizures may complicate the acute phase of a stroke. Seizures are usually partial, with or without secondary generalisation. The recurrence rate is low for seizures occurring shortly after the stroke, but higher for those with a later onset (3%–5% of all cases); 54% to 55% of patients who experience late-onset seizures will develop epilepsy.[79,80] Antiepileptic agents should only be used for recurring seizures, and prophylactic use of these drugs is not indicated in patients who have never had seizures. First-generation antiepileptic drugs, especially phenytoin, are not the most appropriate during the acute phase of stroke because they may interfere with the patient's recovery. Lamotrigine and gabapentin have been evaluated as treatment for post-stroke seizures, and their efficacy/safety profiles are better than those of carbamazepine, oxcarbazepine, or topiramate due to having fewer drug interactions (level of evidence 1a).[80,81] Levetiracetam seems to be useful in patients with late-onset post-stroke seizures, and it may also be effective in the acute phase (level of evidence 3b).[82,83]

Recommendations

1. Patients with extensive anterior territory infarcts or cerebellar infarcts should be monitored closely, and doctors are recommended to use general techniques for preventing oedema (level of evidence 3b; grade B recommendation).
2. Corticosteroids should not be used in cerebral oedema caused by ischaemia (level of evidence 1a; grade A recommendation).
3. If clinical and imaging signs of MMCAI are present, doctors should consider decompressive hemicraniectomy within 48 hours of stroke onset in patients younger than 60 and where signs of transtentorial herniation are absent. Osmotherapy and hyperventilation are to be carried out in preparation for this procedure (level of evidence 1a; grade A recommendation).
4. Suboccipital decompressive craniectomy is recommended in cases of cerebellar infarct in which the brainstem is affected due to compression or obstructive hydrocephalus (level of evidence 3b; grade B recommendation).
5. Prophylactic use of antiepileptic drugs is not recommended in patients with no previous history of seizures (level of evidence 1a; grade A recommendation). Antiepileptics should be administered to patients with recurring seizures (level of evidence 1a; grade A recommendation). Data are insufficient to indicate any single antiepileptic drug as a first-choice treatment.

Prevention and treatment of non-neurological complications

Infections

The most frequent infections are pneumonia and urinary tract infection. Pneumonia develops in patients with an

Table 3 Decompressive craniectomy in malignant infarct of the medial cerebral artery.

Indications

- Age ≤ 60 years.
- Symptom onset ≤ 48 hours.
- Clinical, radiological, and neurosonological signs of extensive MCA infarct or carotid infarct (TACI)
  - NIHSS > 15 at time of admission.
  - After admission, decline in neurological condition (≥4 points on NIHSS) and or level of consciousness (≥1 point on NIHSS item 1a) when other non-neurological causes have been ruled out.
  - Infarct volume ≥ 145 cm^3 determined by diffusion MRI, or:
    - CT showing impairment of ≥50% of the MCA, especially if mass effect is present.
    - Increase in mass effect compared to baseline CT scan.
  - Neurosonology or angiography indicative of occluded carotid or M1 segment of the MCA.
- Stable haemodynamic situation.
- Informed consent signed by family member or representative.

Contraindications or exclusion criteria

- Age > 60 years.
- Poor baseline condition prior to stroke; Rankin score > 2.
- Neurological impairment due to other treatable causes.
- Concomitant illnesses that are severe and/or have a poor prognosis of survival.
- Clotting disorders or elevated risk of haemorrhage.
- Contraindication for anaesthesia.
- Clinical or radiological data for cerebral herniation or brain death.
- Consent not given by family member or representative.
- Patient left express instructions in a living will or other instrument to refuse care that would permit survival with loss of autonomy.

MCA: middle cerebral artery; NIHSS: National Institute of Health Stroke Scale; MRI: magnetic resonance imaging; TACI: total anterior circulation infarct; CT: computed tomography.

altered level of consciousness, decreased cough reflex, or dysphagia. This disease is a significant cause of death in stroke patients. Doctors must identify patients at risk for pneumonia and employ preventative measures such as lung isolation where necessary, respiratory physiotherapy, aspiration of secretions, and preventing vomiting.

Urinary tract infections may cause sepsis in up to 5% of all stroke patients. These infections are more frequent in women and patients with more severe strokes. Doctors recommend avoiding situations, such as urinary catheterisation, that can favour these infections, except where strictly necessary.[84]

Presence of fever indicates that the patient must be checked for pneumonia or UTI; if either is suspected, antibiotic treatment should be started shortly thereafter (level of evidence 2b).[84] Empirical antibiotic treatment is recommended, using amoxicillin/clavulanate at high doses (1—2 g IV/8 h) since this antibiotic covers most microbes that could be responsible. Patients allergic to that treatment should use quinolones (ciprofloxacin 200—400 mg/12 h). Treatment should be adjusted to fit the culture findings or symptoms if there is no response.

Deep vein thrombosis is another common complication. It sometimes provokes pulmonary thromboembolism, which in turn causes death in 25% of stroke cases. Administering low molecular weight heparin is an effective means of preventing venous thrombosis (level of evidence 1a).[85] Aspirin has also proved its efficacy for preventing pulmonary thromboembolism (level of evidence 1a).[86,87] There is no evidence that physical devices, such as compression stockings or intermittent pneumatic compression systems, significantly reduce the incidence of venous thrombosis (level of evidence 1a).[88]

Recommendations

1. Early delivery of antibiotic treatment is recommended for infectious complications (level of evidence 2b; grade B recommendation).
2. Low molecular weight heparin or heparinoids are recommended to prevent deep vein thrombosis and pulmonary embolism in immobilised patients. If these treatments are contraindicated or an alternative is required, aspirin may be used (level of evidence 1a; grade A recommendation).

Specific treatment for cerebral ischaemia in acute stroke

Depending on the type of cerebral ischaemia, there are 2 theoretical approaches to limiting brain damage. These approaches are improving or re-establishing cerebral blood flow (CBF) in the ischaemic area, and employing drugs intended to inhibit the cellular and molecular alterations that lead to ischaemia-reperfusion injury in the potentially salvageable area or ischaemic penumbra (pharmacological brain protection).[89] Both therapeutic strategies must be implemented in early stages to prevent the irreversible progression of different lesion mechanisms. Doctors recently advanced the concept of damage repair based on the

potential existence of plasticity phenomena that may be activated or reinforced through therapeutic interventions.[90,91] Treatments employed for this purpose may have a wider window of opportunity.

Measures intended to improve or re-establish CBF

Ensuring the proper perfusion pressure to maintain a stable haemodynamic situation in the ischaemic area is a crucial target. Antithrombotic and thrombolytic drugs and mechanical thrombectomy have all been used to recanalise and reperfuse ischaemic tissue.

Antithrombotic agents

Anticoagulants Heparin is used in the acute phase of cerebral ischaemia because of its potential effects, which are stopping thrombus progression or promoting thrombus resolution, and preventing early stroke recurrence in cases of ischaemic stroke caused by embolic mechanisms.

Unfractionated heparin Results from the International Stroke Trial (IST) show that administering subcutaneous heparin calcium does not improve patient outcomes. Although this treatment does prevent early recurrence, that effect is counteracted by an associated increased risk of haemorrhage, which is especially pronounced if aspirin is also used (level of evidence 1b).[86] Similarly, a subanalysis within this study was unable to show any benefits of heparin treatment among patients with atrial fibrillation.[92] Other studies evaluating heparin sodium (partial thromboplastin time 1.5—2 times the control) show efficacy for preventing early recurrences in patients with cerebral infarcts of cardioembolic origin,[93,94] but this efficacy comes at the expense of an increase in haemorrhages.

Intravenous heparin has not demonstrated any benefits in cases of progressive cerebral infarct.[95]

A meta-analysis of studies of unfractionated heparin as acute-phase treatment for strokes of all aetiologies revealed no overall benefits.[96] While the meta-analysis found a decreased incidence of deep vein thrombosis, pulmonary thromboembolism, and early stroke recurrence, any benefits were cancelled out by the increased risk of potentially severe haemorrhage (level of evidence 1a). A meta-analysis of studies specifically evaluating heparin use in patients with acute-phase cardioembolic infarct[97] concludes that heparin, compared to aspirin or placebo, does not significantly decrease mortality, dependency, or stroke recurrence in the first 14 days. In addition, it causes a nearly threefold increase in the frequency of symptomatic cerebral haemorrhages. Furthermore, it produces no significant reduction in cases of deep vein thrombosis or pulmonary embolism compared to aspirin (level of evidence 1a).

Low molecular weight heparin and heparinoids

Numerous trials have studied the effect of LMW heparin and heparinoids on acute ischaemic stroke, and overall results have been negative. In a study with nadroparin (FISS), researchers observed a lower 6-month mortality rate among patients receiving treatment.[98] However, these results were not confirmed by a later European clinical trial (FISS bis) which also showed a higher rate of haemorrhagic complications at higher doses.[99] The TOAST clinical trial (Trial of Org 10172 in Acute Stroke Treatment), employing intravenous danaparoid treatment within 24 hours of a cerebral infarct, showed a lower number of haemorrhages among treated patients, but no benefits with regard to preventing stroke progression and early recurrence, or a more favourable outcome at 3 months.[100] Other studies comparing dalteparin[101] or tinzaparin[102] to aspirin have delivered similar results. Meta-analyses of studies of heparinoids and low-molecular weight heparins show that although these treatments lower the incidence of deep vein thrombosis and pulmonary thromboembolism, they do not improve outcomes or decrease early stroke recurrence. They may also cause an increase in intracranial haemorrhages (level of evidence 1a).[85,103]

Studies of the defibrinogenating drug ancrod have revealed no benefits and an increased risk of cerebral haemorrhage.[104,105]

Antiplatelet drugs

The only antiplatelet drug to have been studied in the acute phase of cerebral stroke is aspirin. The International Stroke Trial (IST)[86] and the Chinese Acute Stroke Trial (CAST)[87] show that administering aspirin dosed at 300 mg/day in the first 48 hours and in the first 2 weeks was beneficial for patient outcomes at 6 months. The treatment also reduced early recurrence and mortality rates. Meta-analysis of both studies shows an absolute decrease of 0.7% in the recurrence rate and of 0.4% in the mortality rate. The increase in haemorrhages was 0.2%. The overall benefit was an absolute decrease of 0.9% in the risk of death or recurrence (level of evidence 1a).[106]

Other intravenously administered antiplatelet drugs, such as abciximab or tirofiban, have been studied both in monotherapy and combined with thrombolysis as means of achieving arterial recanalisation in acute cerebral infarct.[107,108] Despite some promising early results, clinical trials with abciximab in the first 6 hours after stroke onset[109] show an increase in the rate of haemorrhages among treated patients (evidence level 1b).[110]

In all clinical trials employing thrombolysis, no antithrombotic agents were administered until 24 hours after delivering the thrombolytic drug, as is currently recommended.

Recommendations

1. Aspirin is recommended in the first 48 hours following a cerebral infarct except where contraindicated (evidence level 1a; grade A recommendation). Early treatment with anticoagulants is not recommended for patients with acute cerebral infarct (evidence level 1a; grade A recommendation).
2. For patients undergoing thrombolysis, no antithrombotic drug should be used until 24 hours after the procedure (evidence level 1a; grade B recommendation).

Thrombolytic drugs and mechanical thrombectomy

At present, we have sufficient evidence, based on randomised studies (NINDS, ECASS, ATLANTIS),[111–115] meta-analysis of these clinical trials,[116–118] and post-marketing clinical practice studies,[119,120] to recommend thrombolytic treatment with intravenous recombinant tissue plasminogen activator (rtPA) dosed at 0.9 mg/kg in acute stroke patients at less than 4.5 hours after onset of a cerebral infarct. This treatment is linked to better clinical and functional outcomes at the 3-month mark (level of evidence 1a).[1,10,111,120] Haemorrhagic complications, particularly symptomatic cerebral haemorrhage, are the main risk in rtPA treatment. The rate of symptomatic cerebral haemorrhage in the SITS_ISTR registry, containing nearly 24 000 patients, was 2%.[120] In general, the rate of haemorrhagic complications decreases and treatment has an appropriate safety margin if dosing recommendations and patient selection criteria are followed strictly (Table 2).

At present, age > 80 years is not considered an exclusion factor for thrombolytic treatment. The frequency of favourable functional outcomes among SITS patients older than 80 and treated with IV rtPA was significantly higher than in patients from trials employing neuroprotection and no thrombolysis (VISTA registry). The effect was similar to that in younger patient groups (level of evidence 2a).[121]

Doctors have also questioned whether prior stroke with diabetes mellitus should be an exclusion factor.[122]

Epileptic seizures at the time of stroke onset increase the likelihood of a diagnostic error, but it is understood that seizures do not constitute a reason for denying thrombolytic treatment if the infarct is confirmed by neuroimaging techniques.[123,124]

The sooner thrombolysis is performed, the greater its benefits,[117] which is why all unnecessary delays are to be avoided.

We do not recommend administering other thrombolytic agents systemically, since this practice is associated with a high rate of haemorrhagic complications (evidence level 1a).[1,10]

Up to a third of the patients treated with intravenous thrombolysis present artery reocclusion. This is more frequent in cases in which recanalisation is incomplete or when an extracranial/intracranial tandem lesion is present.[125] Various strategies have been studied to improve the recanalisation rate after intravenous thrombosis and decrease the frequency of reocclusion. The CLOTBUST study shows that applying ultrasound to the occluded artery while simultaneously administering rtPA improves the recanalisation rate and patient outcomes (level of evidence 1b).[126] Researchers have also observed that simultaneous administration of echo-enhancing agents can improve the recanalisation rate, but doubts remain as to the safety of the procedure (level of evidence 1b).[127] Other treatments designed to prevent reocclusion, such as associating rtPA with anticoagulants (tirofiban, argatroban) or fast-acting antiplatelet drugs (abciximab, eptifibatide), did not return favourable results.[107,108,128]

Clinical trials are currently examining other synthetic thrombolytic agents (desmoteplase, reteplase, tenecteplase) which have been modified for better thrombolytic capacity and increased affinity and selectivity for thrombin bound to the thrombus in order to reduce associated haemorrhagic complications. Results are promising but not yet confirmed.[129–133]

Results from studies evaluating the utility of intra-arterial thrombolysis, whether in monotherapy or in combination with intravenous thrombolysis, are promising, and studies continue. Nevertheless, endovascular techniques are becoming increasingly common in daily clinical practice. Available evidence is based on only a very few randomised controlled trials in addition to some case series and prospective registry studies. Based on existing data from the randomised, placebo-controlled PROACT II trial, intra-arterial thrombolysis with recombinant pro-urokinase is an effective means of recanalising arteries occluded by thrombus, and applying that treatment is linked to a higher percentage of patients being independent at 3 months. It increases the risk of cerebral haemorrhaging, but not of mortality (level of evidence 1b).[134,135] Despite the above, it was not approved by regulatory authorities. The procedure necessarily involves a longer delay in administering treatment. At present, no data support the premise that intra-arterial thrombolysis offers better outcomes than intravenous thrombolysis, although the technique has been used in patients with large vessel occlusions, patients with salvageable tissue at more than 4.5 hours after stroke onset, and where intravenous thrombolysis was contraindicated (evidence level 2b). The therapeutic window would be 6 hours from stroke onset for the anterior territory (level of evidence 1b), 12 hours for the posterior territory, and up to 24 hours in cases with progressive or fluctuating onset. However, some case series include patients with posterior territory strokes treated as much as 48 hours after onset (level of evidence 4).[136–139]

The sparse data on combining intravenous and intra-arterial thrombolysis suggest that this treatment may be safe.[140,141] The IMS I study found that a partial dose of intravenous rtPA followed by intra-arterial thrombolysis yielded functional outcomes that were better than those in historical controls in the NINDS trial, but no better than outcomes in NINDS trial patients who had received thrombolytic agents (level of evidence 1b).[142] The IMS III study, which is in progress and has recruited more than 300 patients, evaluates whether intravenous thrombolysis plus endovascular intervention (intra-arterial thrombolysis or mechanical device) is more beneficial than intravenous treatment alone.[143]

It is also possible to perform mechanical thrombectomy using intra-arterial devices that break up and extract the blood clot. The MERCI study reported recanalisation in 45% of the patient total. This rate was 64% in the group receiving combined treatment with intra-arterial rtPA. Fifty per cent of the recanalised patients improved significantly. Nevertheless, clinical outcomes were no better than those reported by the PROACT study.[144] The Multi-MERCI study reported recanalisation in 55% of the cases; 3-month outcome was good in 36% of the patients. There was also a significant increase in haemorrhages and a 34% mortality rate, which could be linked to the fact that these patients had suffered severe strokes.[145] In a combined analysis of the MERCI and Multi MERCI studies compared to PROACT II, researchers concluded that results from embolectomy were similar to those from the PROACT II treatment group, and the mortality rate also resembled that in the PROACT II control group.[146] The

single-arm study of the PENUMBRA device yielded better results than the MERCI study, with a recanalisation rate of 81% and no significant increases in mortality. Clinical outcomes, however, were poor. The percentage of patients with favourable clinical outcomes resembled the rate in the PROACT study control group.[147] Multiple randomised and prospective registry studies are underway to evaluate the efficacy and safety of numerous mechanical thrombectomy devices for use in both the anterior and posterior territories. Today, mechanical intra-arterial recanalisation procedures may be considered an option in patients in whom intravenous thrombolysis is contraindicated, provided that salvageable tissue remains. The therapeutic window is 8 hours for the anterior territory (level of evidence 1b). Although the posterior territory is less commonly affected, the therapeutic window in these cases may be the same as in intra-arterial pharmacological thrombolysis (level of evidence 4). These procedures should only be carried out in centres with the proper equipment and experience.[138]

Recommendations

1. Thrombolytic treatment with IV rtPA dosed at 0.9 mg/kg is recommended as treatment for acute cerebral infarct up to 4.5 hours after stroke onset. Treatment should be performed as early as possible. Patient selection should follow established criteria strictly. Guidelines for administering treatment, and for treating arterial hypertension or haemorrhagic complications, are shown in Table 3 (level of evidence 1a; grade A recommendation).
2. Treatment must be indicated by neurologists with expertise in stroke management and performed in centres equipped to provide specialist care, preferably in an SU. These centres must also be able to treat potential complications (extrapolation from Level 1 studies; grade B recommendation).
3. Antithrombotic drugs (heparin, aspirin) are not recommended in the 24 hours following IV thrombolysis (extrapolation from Level 1 studies; grade B recommendation).
4. Intra-arterial thrombolysis may be useful in patients with large-vessel occlusion stroke, and who are not candidates for intravenous thrombolysis, until 6 hours post-infarct (level of evidence 1b; grade B recommendation).
5. The utility of combined intra-arterial and intravenous treatment has not yet been established, but it may be an option for patients presenting large-vessel occlusion who do not respond to intravenous treatment (evidence level 2b; grade B recommendation).
6. Mechanical thrombolysis may be useful until 8 hours post-stroke in patients who are not candidates for intravenous thrombolysis or who have experienced treatment failure (level of evidence 1b; grade B recommendation).
7. At present, endovascular treatment is only recommended when performed in centres with SUs and experience in neurointervention. Ideally, this procedure is performed according to a case registry or clinical study protocol (level of evidence 5; grade D recommendation).

Cerebral protection and reparation

Pharmacological cerebral protection Progress in our understanding of the cellular and molecular changes underlying the pathophysiology of cerebral ischaemia has sparked investigations into multiple drugs that may be able to prevent these changes, and therefore inhibit the mechanisms responsible for damage due to cerebral ischaemia and reperfusion. This capacity is known as 'neuroprotection' or 'pharmacological cerebral protection'.[1,110,148,149] Researchers have studied numerous pharmacological agents known as neuroprotectors; at least in theory, these agents may lessen the damage caused by interruption of the CBF by inhibiting one or more of the biochemical mediators of ischaemia-reperfusion damage. Many of the more than 1000 completed experimental studies have shown positive results, although these results were not confirmed by most of the 400 clinical studies that have since been performed (Table 4). The lack of clinical confirmation for results from experimental studies is partially due to poor adaptation between basic translational research strategies and clinical trial design.[150] We will not provide detailed descriptions of all clinical trials for each of these different drugs because this exceeds the scope of these guidelines. Instead, we will focus on those drugs for which trials are still underway and on drugs that may be clinically useful based on their promising results.

Citicoline Citicoline is an intermediary of phosphatidylcholine synthesis. It facilitates acetylcholine synthesis in the brain, reduces accumulation of free fatty acids in ischaemic tissue, and displays antioxidant activity.[183] Numerous clinical trials have shown that citicoline administered in the first 24 hours after stroke onset can deliver favourable outcomes. The best dosage seems to be 2000 mg/day during 6 weeks.[184–187] These data suggest that citicoline has a therapeutic effect[188] (level of evidence 2b), and they are being investigated in a new phase-III trial, the ICTUS study.[110,189]

High-dose human serum albumin Many of albumin's activities may exert a protective effect,[149] and albumin has shown its efficacy in experimental studies. The ALIAS I clinical study was a small pilot study of escalating doses in which human albumin was administered to patients in the first 16 hours after stroke. An analysis comparing outcomes between treated patients and historical controls from the NINDS study showed that patients receiving higher doses of albumin in addition to thrombolytic treatment were 3 times more likely to have a favourable outcome (level of evidence 2b).[199] To investigate these data, another phase-III study is being carried out at present.[110,200]

Minocycline Minocycline is a tetracycline-derived antibiotic. Experimental studies of this drug point to a protective effect mediated by its anti-inflammatory and anti-apoptotic activity. A small clinical trial found that patients treated

Table 4 Pharmacological cerebral protection in cerebral ischaemia: clinical trials.

Drugs	Action mechanism	Result
Drugs acting on ion channel receptors		
Ca^{2+} channel blockers		
Nimodipine[151–153,158]	Dihydropyridine	No efficacy/adverse effects
Nicardipine[154]	"	No efficacy/adverse effects
Darodipine[155]	"	No efficacy
Isradipine[156]	"	Adverse effects
Flunarizine[157]	"	No efficacy/adverse effects
Other ionic channel blockers		
BMS-204352[110,159]	MaxiK channel blocker	No efficacy
Antagonists of NMDA/AMPA-sensitive glutamate receptors		
Selfotel[160]	Competitive NMDA receptor antagonist	Adverse effects
Dextrorphan[161]	Non-competitive NMDA receptor antagonist	Adverse effects
Aptiganel[162]	"	Adverse effects
Magnesium[110,149,163]	Non-competitive NMDA receptor antagonist	No efficacy
	Calcium channel blocker	Phase III in progress
Gavestinel[164,165]	Glycine-site antagonist	No efficacy
Drugs acting on neurotransmission		
Inhibitors of pre-synaptic glutamate release		
Lubeluzole[166,167]	Na^+ channel blocker, modulates NOS pathway	No efficacy
Inhibitors of other neurotransmitters		
Clomethiazole[168–170]	GABA agonist	No efficacy
Diazepam[171]	GABA agonist	No efficacy
BAYx3702 (Repinotan)[110]	5-HT agonist	No efficacy
Nalmefene (Cervene)[172]	Kappa-selective opioid antagonist	No efficacy
Antioxidant drugs free radical inhibitors		
Tirilazad[173–176]	Inhibits lipid peroxidation, iron loading	No efficacy/adverse effects
Ebselen[110,177]	Similar activity to glutathione peroxidase	Questionable
Edaravone[178]	Inhibits lipid peroxidation	Phase II. No efficacy
NXY-059[179,180]	Proton trapping agent	Not effective
DP-b99 (MACSI)[110]	Metal ion trapping agent	Under study
Inflammatory response modulators		
Enlimomab[181]	Anti-ICAM 1 antibodies	Adverse effects
UK 279,276[182]	Inhibitor of CD11b/CD18 receptor	No efficacy
Drugs with trophic and/or repair activity		
Citicoline[183–189]	Phosphatidylcholine synthesis	Phase II inconclusive Phase III underway
Piracetam[190]	Promotes membrane fluidity	No efficacy
Neurotrophic factors		
bFGF[191]	Basic fibroblastic growth factor	No efficacy
GM-1[192]	Monosialoganglioside	No efficacy/adverse effects
Cerebrolysin[193–195]	Brain-derived peptides	Phase II inconclusive Phase III underway
Miscellaneous		
Haemodilution[196–198]	No efficacy	
Albumin[110,149,199,200]	Antioxidant, protects microvascularisation	Under study
Minocycline[110,201]	Antibiotic with anti-inflammatory activity	Under study
Statins[110,202–206]	Pleiotropic effect	Under study

AMPA: α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; GABA: gamma-aminobutyric acid; NMDA: N-methyl-D-aspartic acid.

with minocycline had better 3-month outcomes than those on a placebo, as measured by the NIHSS score, Barthel index, and modified Rankin scale (level of evidence 2b).[201]

Statins In addition to their lipid-lowering activity, statin drugs exert a protective effect in cerebral ischaemia. Several studies have shown that statin treatment prior to a stroke is associated with better prognosis, and that discontinuing statins is an independent factor for poor prognosis (level of evidence 2b). Some studies indicate that early treatment with statins improves outcomes in acute stroke patients.[202–206] Further studies are currently underway.[110]

Brain repair Brain repair is an endogenous, natural process beginning after injury occurs. It includes processes of cellular proliferation, neurogenesis, angiogenesis, and synaptogenesis, which may be promoted through rehabilitation and the delivery of trophic factors, drugs with trophic effect, and stem cells.[207] The different rehabilitation techniques favour brain plasticity processes, thereby promoting better functional recovery.[57–59] Different trophic factors such as erythropoietin (EPO), granulocyte colony-stimulating factor (GCSF), insulin-like growth factor-1 (IGF-1), or basic fibroblast growth factor (bFGF) have been tested in clinical trials after animal models delivered promising results. Some have had to be interrupted due to adverse effects, while others showed the treatment to be safe, and still others showed a negative effect for these treatments (Table 4).[191,192,208] Drugs exerting a trophic effect, such as citicoline[183,189] or cerebrolysin,[193,195] have also demonstrated activity that favours repair mechanisms.

Regarding cell therapy, different cell lines have been used in animal models of cerebral infarct, and they have yielded good results in the areas of brain repair and functional recovery.[209] In addition, there have been numerous clinical trials in which stem cell transplants in stroke patients have demonstrated safety and tolerability.[91] Many different trials are currently underway to investigate distinct cell lines, which include neural stem cells (CTX0E03) in the PISCES study and the mesenchymal stem cells in the ISIS study.[110,210,211]

Recommendations

1. For ischaemic stroke patients previously treated with statins, those drugs should not be discontinued (level of evidence 2a; grade B recommendation).
2. Patients should begin appropriate rehabilitation programmes as soon as they are in stable condition (level of evidence 1a; grade A recommendation).
3. At present, data are not sufficient to recommend generalised use of any drugs with potential protective or repair activity as treatment for cerebral infarct.
4. Stem cell therapy is currently under investigation and cannot be recommended for clinical practice.

Treatment for cerebral venous thrombosis

Cerebral venous thrombosis has different clinical manifestations that may include headache (the most frequent symptom), visual disorders, papilloedema and altered level of consciousness (if intracranial pressure increases significantly), and venous infarct with focal deficits or convulsions.[212–214]

Radiological tests are fundamental for diagnosis. Compatible signs can usually be observed in a simple CT scan, which is the imaging technique of choice in emergency departments due to its availability. If the cerebral venous thrombosis is suspected, CT is performed with and without contrast. New helical CT scanners perform non-invasive venography; this technique can confirm the presence of thrombosis in venous sinuses and the extent of thrombosis by showing lack of flow in the affected sinus. CT is indicated in suspected cases of cerebral venous thrombosis so that the emergency department can confirm the diagnosis. Magnetic resonance imaging is the most sensitive technique for confirming this type of thrombosis.[213,214] Performing conventional invasive arteriography is rarely necessary.

Doctors will subsequently complete all specific studies needed to determine aetiology (prothrombotic states, clotting disorders, other haematological diseases, drug abuse, autoimmune or connective tissue diseases, cancer, infections, etc.).[214] Any such disorders will be treated specifically.

Some randomised clinical trials have been carried out to test treatments. A small double-blind study compared a placebo to dose-adjusted unfractionated heparin (activated partial thromboplastin time at least twice that of the control). This study, containing only 20 patients, was terminated prematurely after showing better outcomes among patients treated with heparin.[215]

Another randomised study compared nadroparin (90 anti-Xa U/kg/12 h) to a placebo over a 3-week period. After 12 weeks, 13% of the patients in the anticoagulated group (3 of 30) and 21% of the patients in the placebo group (6 of 29) showed poor outcomes; for the nadroparin group, absolute benefit was 7% and reduction in relative risk was 38%. There were no new symptomatic cerebral haemorrhages. Furthermore, the placebo group contained twice as many patients with intracranial hypertension as the nadroparin group (28% vs 13%).[216] Meta-analysis of these 2 studies found that anticoagulation was associated with a lower risk of death or dependency, but the difference was not significant.[217] The studies suggest that the risk of cerebral haemorrhage associated with heparin treatment is low in these patients. They also indicate a low risk of growth when haemorrhage does occur, which indicates that heparin treatment has a favourable risk-to-benefit ratio (level of evidence 1a). A recent non-randomised study including 624 patients suggests that low molecular weight heparin is safer and more effective than unfractionated heparin in patients with cerebral venous thrombosis, especially in patients experiencing haemorrhagic lesions at onset (evidence level 2b).[218]

Regarding other techniques for recanalising thrombosed sinuses, one systematic review suggests that local pharmacological thrombolysis may be beneficial in more severe cases and may even reduce mortality rates (level of evidence 3a).[219] Mechanical thrombectomy is technically feasible, but experience with the technique is only anecdotal at present.[214]

In patients with large parenchymatous lesions and significant mass effects leading to herniation, decompressive craniectomy decreases mortality and is generally associated with good functional outcomes (level of evidence 2b).[220]

Recommendations

1. Anticoagulant treatment with low molecular weight heparin or IV heparin is recommended for cerebral venous thrombosis even in cases with haemorrhagic lesions (level of evidence 1a; grade A recommendation). Low molecular weight heparin is preferable to unfractionated heparin in cases with haemorrhagic lesions (level of evidence 2b; grade B recommendation).
2. Local pharmacological thrombolysis may be an option in severe cases (level of evidence 3a; grade B recommendation.

Conclusion

It is often said that ''time is brain'', and we should not forget that effective treatments are available, such as hospitalisation in an SU, intravenous thrombolysis, and other promising therapies such as neurovascular interventions. Additional treatments are currently being studied.

As we learn from this review, many aspects in the treatment of cerebral infarcts have been thoroughly verified, and their grades of recommendation are therefore high. Nevertheless, numerous potential treatments have yet to be tested. We should adhere closely to guidelines when treating our patients, while also encouraging researchers to complete clinical trials that may yield sufficiently reliable new treatment options. Treating cerebral infarcts according to evidence-based recommendations will ensure safer and more effective management of these processes, and also help unify criteria and reduce care-related costs for these patients.

Funding

This study has received no funding of any kind.

Conflicts of interest

The authors have no conflicts of interest to declare.

Addendum. Ad hoc committee of the SEN Study Group for Cerebrovascular Diseases formed to draw up clinical practice guidelines for stroke

Coordinator: Exuperio Díez-Tejedor, Hospital Universitario La Paz, Madrid.

A.1. *Drafting committee*

Exuperio Díez-Tejedor (Coordinator), Hospital Universitario La Paz, Madrid; Blanca Fuentes (Secretary), Hospital Universitario La Paz, Madrid; María Alonso de Leciñana, Hospital Universitario Ramón y Cajal, Madrid; José Álvarez-Sabin, Hospital Universitari Vall d'Hebron, Barcelona; Juan Arenillas, Hospital Universitario Clínico, Valladolid; Sergio Calleja, Hospital Universitario Central de Asturias, Oviedo; Ignacio Casado, Hospital San Pedro, Cáceres; Mar Castellanos, Hospital Josep Trueta, Girona; José Castillo, Hospital Clínico Universitario, Santiago de Compostela; Antonio Dávalos, Hospital Universitari Germans Trias i Pujol, Badalona; Fernando Díaz-Otero, Hospital Universitario Gregorio Marañón, Madrid; Exuperio Díez-Tejedor, Hospital Universitario La Paz, Madrid; José Antonio Egido, Hospital Clínico Universitario San Carlos, Madrid; Juan Carlos López Fernández, Hospital Universitario Dr. Negrín, Las Palmas; Mar Freijo, Hospital Universitario de Basurto, Bilbao; Blanca Fuentes, Hospital Universitario La Paz, Madrid; Jaime Gállego, Hospital General de Navarra, Pamplona; Andrés García Pastor, Hospital Universitario Gregorio Marañón, Madrid; Antonio Gil-Núñez, Hospital Universitario Gregorio Marañón, Madrid; Francisco Gilo, Hospital Universitario La Princesa, Madrid; Pablo Irimia, Clínica Universitaria de Navarra, Pamplona; Aida Lago, Hospital Universitari La Fe, Valencia; José Maestre, Hospital Universitario Virgen de las Nieves, Granada; Jaime Masjuan, Hospital Universitario Ramón y Cajal, Madrid; Joan Martí-Fábregas, Hospital de la Santa Creu i Sant Pau, Barcelona; Patricia Martínez-Sánchez, Hospital Universitario La Paz, Madrid; Eduardo Martínez-Vila, Clínica Universitaria de Navarra, Pamplona; Carlos Molina, Hospital Universitari Vall d'Hebron, Barcelona; Ana Morales, Hospital Universitario Virgen de la Arrixaca, Murcia; Florentino Nombela, Hospital Universitario La Princesa, Madrid; Francisco Purroy, Hospital Universitari Arnau de Vilanova, Lleida; Marc Ribó, Hospital Universitari Vall d'Hebron, Barcelona; Manuel Rodríguez-Yañez, Hospital Clínico Universitario, Santiago de Compostela; Jaime Roquer, Hospital del Mar, Barcelona; Francisco Rubio, Hospital Universitari de Bellvitge, Barcelona; Tomás Segura, Hospital Universitario de Albacete, Albacete; Joaquín Serena, Hospital Josep Trueta, Girona; Patricia Simal, Hospital Clínico Universitario San Carlos, Madrid; Javier Tejada, Hospital Universitario de León, León; José Vivancos, Hospital Universitario La Princesa, Madrid.

A.2. *Review or institutional committee*

José Álvarez-Sabín, Hospital Universitari Vall d'Hebron, Barcelona; José Castillo, Hospital Clínico Universitario, Santiago de Compostela; Exuperio Díez-Tejedor, Hospital Universitario La Paz, Madrid; Antonio Gil-Núñez, Hospital Universitario Gregorio Marañón, Madrid; José Larracoechea, Hospital de Cruces, Bilbao; Eduardo Martínez-Vila, Clínica Universitaria de Navarra, Pamplona; Jaime Masjuan, Hospital Universitario Ramón y Cajal, Madrid; Jorge Matías-Guiu, Hospital Clínico Universitario San Carlos, Madrid; Francisco Rubio, Hospital de Bellvitge, Barcelona.

References

1. Egido JA, Alonso de Leciñana M, Martínez-Vila E, Díez-Tejedor E, en representación del comité *ad hoc* del Grupo de Estudio de Enfermedades Cerebrovasculares de la Sociedad Española de Neurología. Guía para el tratamiento del infarto cerebral agudo. In: Díez Tejedor E, editor. Guía para el diagnóstico y tratamiento del ictus. Guías Oficiales de la Sociedad Española

de Neurología N.° 3. Prous Science. 2006. ISBN 84-8124-225-X: 97-132.
2. Centre for Evidence Based Medicine. Available from: http://www.cebm.net/ [accessed 2011].
3. Aboderin I, Venables G, Asplund K. Stroke management in Europe. J Intern Med. 1996;240:173—80.
4. Kjellström T, Norrving B, Shatchkute A. Helsingborg Declaration 2006 on European stroke strategies. Cerebrovasc Dis. 2007;23:231—41.
5. Alonso de Leciñana M, Gil Nuñez A, Díez Tejedor E. Relevance of stroke code, stroke unit and stroke networks in organization of acute stroke care. The Madrid Acute Stroke Care Program. Cerebrovasc Dis. 2009;27 Suppl. 1:S140—7.
6. Belvis R, Cocho D, Martí-Fábregas J, Pagonabarraga J, Aleu A, García-Bargo MD, et al. Benefits of a prehospital stroke code system. Feasibility and efficacy in the first year of clinical practice in Barcelona, Spain. Cerebrovasc Dis. 2005;19:96—101.
7. Álvarez-Sabín J, Molina CA, Abilleira S, Montaner J, García Alfranca F, Jiménez Fabrega X, et al. Impacto del código ictus en la eficacia del tratamiento trombolítico. Med Clin (Barc). 2003;120:47—51.
8. Zarza B, Alonso de Leciñana M, García-Barragán N, Díaz-Sánchez M, López-Sendón J, Cruz-Culebras A, et al. Influence of the experience and of out-of-hospital stroke code in thrombolytic treatment of acute stroke. Neurologia. 2008;23:349—55.
9. Acker JE, Pancioli AM, Crocco TJ, Eckstein MK, Jauch EC, Larrabee H, et al. Implementation strategies for emergency medical services within stroke systems of care: a policy statement from the American Heart Association/American Stroke Association Expert Panel on Emergency Medical Services Systems and the Stroke Council. Stroke. 2007;38: 3097—115.
10. Adams HPJJr, Del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. Stroke. 2007;38:1655—711.
11. Dávalos A, Castillo J, Martínez-Vila E, for the Cerebrovascular Disease Study Group of the Spanish Society of Neurology. Delay in neurological attention and stroke outcome. Stroke. 1995;26:2233—7.
12. Goldstein LB, Matchar DB, Hoff-Lindquist J, Samsa GP, Horner RD. VA Stroke Study: neurologist care is associated with increased testing but improved outcomes. Neurology. 2003;61:792—6.
13. Schwamm LH, Holloway RG, Amarenco P, Audebert HJ, Bakas T, Chumbler NR, et al. Interdisciplinary Council on Peripheral Vascular Disease. A review of the evidence for the use of telemedicine within stroke systems of care: a scientific statement from the American Heart Association/American Stroke Association. Stroke. 2009;40:2616—34.
14. Lanska DJ, the Task Force on Hospital Utilization for Stroke of the American Academy of Neurology. Review criteria for hospital utilization for patients with cerebrovascular disease. Neurology. 1994;44:1531—2.
15. Indredavik B, Bakke F, Solberg R, Rokseth R, Haaheim Ll, Holme I. Benefit of a stroke unit: a randomized controlled trial. Stroke. 1991;22:1026—31.
16. Stroke Unit Trialists' Collaboration. Organised inpatient (stroke unit) care for stroke. Cochrane Database Syst Rev. 2002;1:CD000197.
17. Lanhorne P, Williams BO, Gilchrist W, Howie K. Do stroke units save lives? Lancet. 1993;342:395—8.
18. Egido JA, González JL, Varela de Seijas E. Experiencia de una Unidad de Ictus en el Hospital Clínico de Madrid. Rev Neurol. 1995;23:381—4.
19. Díez-Tejedor E, Fuentes B. Acute care in stroke: do stroke units make the difference? Cerebrovasc Dis. 2001;11 Suppl. 1:S31—9.
20. Govan L, Langhorne P, Weir CJ, Stroke Unit Trialists Collaboration. Does the prevention of complications explain the survival benefit of organized inpatient (stroke unit) care? Further analysis of a systematic review. Stroke. 2007;38:2536—40.
21. Díez-Tejedor E, Fuentes B. Homeostasis as basis of acute stroke treatment: stroke units are the key. Cerebrovasc Dis. 2005;20 Suppl. 2:S129—34.
22. Seenan P, Long M, Langhorne P. Stroke units in their natural habitat: systematic review of observational studies. Stroke. 2007;38: 1886—92.
23. Fuentes B, Díez Tejedor E. Stroke units. Many questions, some answers. Int J Stroke. 2009;4:28—37.
24. Álvarez Sabín J, Alonso de Leciñana M, Gállego J, Gil Peralta A, Casado I, Castillo J, et al. Plan de atención sanitaria al ictus. Neurologia. 2006;21:717—26.
25. Masjuan J, Álvarez-Sabín J, Arenillas J, Calleja S, Castillo J, Dávalos A, et al. Plan de asistencia sanitaria al ictus II 2010. Neurologia. 2011;26:383—96.
26. Rowat AM, Dennis MS, Wardlaw JM. Hypoxaemia in acute stroke is frequent and worsens outcome. Cerebrovasc Dis. 2006;21:166—72.
27. Roffe C, Sills S, Pountain SJ, Allen M. A randomized controlled trial of the effect of fixed-dose routine nocturnal oxygen supplementation on oxygen saturation in patients with acute stroke. J Stroke Cerebrovasc Dis. 2010;19:29—35.
28. Oliveira-Filho J, Silva SC, Trabuco CC, Pedreira BB, Sousa EU, Bacellar A. Detrimental effect of blood pressure reduction in the first 24 hours of acute stroke onset. Neurology. 2003;61:1047—51.
29. Castillo J, Leira R, García MM, Serena J, Blanco M, Dávalos A. Blood pressure decrease during the acute phase of ischemic stroke is associated with brain injury and poor stroke outcome. Stroke. 2004;35:520—6.
30. Leira R, Millán M, Díez-Tejedor E, Blanco M, Serena J, Fuentes B, et al. Age determines the effects of blood pressure lowering during the acute phase of ischemic stroke: the TICA study. Hypertension. 2009;54:769—74.
31. Vemmos KN, Tsivgoulis G, Spengos K, Zakopoulos N, Synetos A, Manios E, et al. U-shaped relationship between mortality and admission blood pressure in patients with acute stroke. J Intern Med. 2004;255:257—65.
32. International Society of Hypertension Writing Group. International Society of Hypertension: statement on the management of blood pressure in acute stroke. J Hypertens. 2003;21:665—72.
33. Schrader J, Luders S, Kulschewski A, Berger J, Zidek W, Treib J, et al. The ACCESS study: evaluation of acute candesartan cilexitil therapy in stroke survivors. Stroke. 2003;34:1699—703.
34. Blood pressure in Acute Stroke Collaboration (BASC). Interventions for deliberately altering blood pressure in acute stroke. Cochrane Database Syst Rev. 2001;(2), doi:10.1002/14651858.CD000039. Art. no.: CD000039.
35. Potter JF, Robinson TG, Ford GA, Mistri A, James M, Chernova J, et al. Controlling hypertension and hypotension immediately post-stroke (CHHIPS): a randomised, placebo-controlled, double-blind pilot trial. Lancet Neurol. 2009;8:48—56.
36. Robinson TG, Potter JF, Ford GA, Bulpitt CJ, Chernova J, Jagger C, et al. Effects of antihypertensive treatment after acute stroke in the Continue or Stop Post-Stroke Antihypertensives Collaborative Study (COSSACS): a prospective, randomised,

open, blinded-endpoint trial. Lancet Neurol. 2010;9:767—75.
37. Sandset EC, Bath PM, Boysen G, Jatuzis D, Kõrv J, Lüders S, SCAST Study Group. The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST): a randomised, placebo-controlled, double-blind trial. Lancet. 2011;377:741—50.
38. Castillo J, Martínez F, Leira R, Prieto JM, Lema M, Noya M. Mortality and morbidity of acute cerebral infarction related with temperature and basal analytic parameters. Cerebrovasc Dis. 1994;4:66—71.
39. Hajat C, Hajat S, Sharma P. Effects of poststroke pyrexia on stroke outcome: a meta-analysis of studies in patients. Stroke. 2000;31:404—9.
40. Den Hertog HM, Van der Worp HB, Van Gemert HM, Algra A, Kappelle LJ, Van Gijn J, et al. The Paracetamol (Acetaminophen) In Stroke (PAIS) trial: a multicentre, randomised, placebo-controlled, phase III trial. Lancet Neurol. 2009;8:434—40.
41. Den Hertog HM, van der Worp HB, Tseng MC, Dippel DW. Cooling therapy for acute stroke. Cochrane Database Syst Rev. 2009;21:CD001247.
42. Macleod MR, Petersson J, Norrving B, Hacke W, Dirnagl U, Wagner M, et al. Hypothermia for stroke: call to action 2010. Int J Stroke. 2010;5:489—92.
43. van der Worp HB, Macleod MR, Kollmar R, European Stroke Research Network for Hypothermia (EuroHYP). Therapeutic hypothermia for acute ischemic stroke: ready to start large randomized trials? J Cereb Blood Flow Metab. 2010;30:1079—93.
44. Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. Stroke. 2001;32:2426—32.
45. Baird TA, Parsons MW, Phanh T, Butcher KS, Desmond PM, Tress BM, et al. Persistent poststroke hyperglycemia is independently associated with infarct expansion and worse clinical outcome. Stroke. 2003;34:2208—14.
46. Fuentes B, Castillo J, San José B, Leira R, Serena J, Vivancos J, et al. The prognostic value of capillary glucose levels in acute stroke: the GLycemia in Acute Stroke (GLIAS) study. Stroke. 2009;40:562—8.
47. Fuentes B, Ortega-Casarrubios MA, Sanjosé B, Castillo J, Leira R, Serena J, et al. Persistent hyperglycemia > 155 mg/dL in acute ischemic stroke patients: how well are we correcting it? Implications for outcome. Stroke. 2010;41:2362—5.
48. Álvarez-Sabín J, Molina CA, Montaner J, Arenillas JF, Huertas R, Ribo M, et al. Effects of admission hyperglycemia on stroke outcome in reperfused tissue plasminogen activator-treated patients. Stroke. 2003;34:1235—41.
49. Ribo M, Molina C, Montaner J, Rubiera M, Delgado-Mederos R, Arenillas JF, et al. Acute hyperglycemia state is associated with lower tPA-induced recanalization rates in stroke patients. Stroke. 2005;36:1705—9.
50. Gray CS, Hildreth AJ, Sandercock PA, O'Connell JE, Johnston DE, Cartlidge NE, et al. 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.
51. Bruno A, Kent TA, Coull BM, Shankar RR, Saha C, Becker KJ, et al. Treatment of hyperglycemia in ischemic stroke (THIS): a randomized pilot trial. Stroke. 2008;39:384—9.
52. Davalos A, Ricart W, Gonzalez-Huix F, Soler S, Marrugat J, Molins A, et al. Effect of malnutrition after acute stroke on clinical outcome. Stroke. 1996;27:1028—32.
53. FOOD Trial Collaboration. Poor nutritional status on admission predicts poor outcomes after stroke: observational data from the FOOD trial. Stroke. 2003;34:1450—6.
54. Dennis MS, Lewis SC, Warlow C, FOOD Trial Collaboration. Effect of timing and method of enteral tube feeding for dysphagic stroke patients (FOOD): a multicentre randomised controlled trial. Lancet. 2005;365:764—72.
55. Kwakkel G, Wagenaar RC, Koelman TW, Lankhorst GJ, Koetsier JC. Effects of intensity of rehabilitation after stroke. A research synthesis. Stroke. 1997;28:1550—6.
56. Langhorne P, Wagenaar R, Partridge C. Physiotherapy after stroke: more is better? Physiother Res Int. 1996;1:75—88.
57. Langhorne P, Duncan P. Does the organization of postacute stroke care really matter? Stroke. 2001;32:268—74.
58. Goldstein LB. Potential effects of common drugs on stroke recovery. Arch Neurol. 1998;55:454—6.
59. Chollet F, Tardy J, Albucher JF, Thalamas C, Berard E, Lamy C, et al. Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial. Lancet Neurol. 2011;10:123—30.
60. Zittel S, Weiller C, Liepert J. Citalopram improves dexterity in chronic stroke patients. Neurorehabil Neural Repair. 2008;22:311—4.
61. Hackett ML, Anderson CS, House A, Xia J. Interventions for treating depression after stroke. Cochrane Database Syst Rev. 2008;4:CD003437.
62. van der Worp HB, Kappelle LJ. Complications of acute ischaemic stroke. Cerebrovasc Dis. 1998;8:124—32.
63. Hacke W, Schwab S, Horn M, Spranger M, De Georgia M, von Kummer R. Malignant middle cerebral artery territory infarction: clinical course and prognostic signs. Arch Neurol. 1996;53:309—15.
64. Berrouschot J, Sterker M, Bettin S, Koster J, Schneider D. Mortality of space-occupying (malignant) middle cerebral artery infarction under conservative intensive care. Intensive Care Med. 1998;24:620—3.
65. Schwarz S, Georgiadis D, Aschoff A, Schwab S. Effects of body position on intracranial pressure and cerebral perfusion in patients with large hemispheric stroke. Stroke. 2002;33:497—501.
66. Bauer RB, Tellez H. Dexamethasone as treatment in cerebrovascular disease. A controlled study of acute cerebral infarction. Stroke. 1973;4:547—55.
67. Norris JW, Hachinski V. High dose steroid treatment in cerebral infarction. Br Med J. 1986;292:21—3.
68. Qizilbash N, Lewington SL, López-Arrieta JM. Corticosteroids for acute ischaemic stroke. Cochrane Database Syst Rev. 2002;2:CD000064.
69. Bereczki D, Liu M, do Prado GF, Fekete I. Cochrane report: a systematic review of mannitol therapy for acute ischemic stroke and cerebral parenchymal hemorrhage. Stroke. 2000;31:2719—22.
70. Bereczki D, Mihálka L, Szatmári S, Fekete K, Di Cesar D, Fülesdi B, et al. Mannitol use in acute stroke: case fatality at 30 days and 1 year. Stroke. 2003;34:1730—5.
71. Righetti E, Celani MG, Cantisani T, Sterzi R, Boysen G, Ricci S. Glycerol for acute stroke. Cochrane Database Syst Rev. 2004;2:CD000096.
72. Jüttler E, Schwab S, Schmiedek P, Unterberg A, Hennerici M, Woitzik J, et al. Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery (DESTINY): a randomized, controlled trial. Stroke. 2007;38:2518—25.
73. Vahedi K, Vicaut E, Mateo J, Kurtz A, Orabi M, Guichard JP, et al. Sequential-design, multicenter, randomized, controlled

trial of early decompressive craniectomy in malignant middle cerebral artery infarction (DECIMAL Trial). Stroke. 2007;38:2506—17.
74. Vahedi K, Hofmeijer J, Juettler E, Vicaut E, George B, Algra A, 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.
75. Hofmeijer J, Kappelle LJ, Algra A, Amelink GJ, Van Gijn J, Van der Worp HB. Surgical decompression for space-occupying cerebral infarction (the Hemicraniectomy After Middle Cerebral Artery infarction with Life-threatening Edema Trial [HAMLET]): a multicentre, open, randomised trial. Lancet Neurol. 2009;8:326—33.
76. Staykov D, Gupta R. Hemicraniectomy in malignant middle cerebral artery infarction. Stroke. 2011;42:513—6.
77. Schwab S, Aschoff A, Spranger M, Albert F, Hacke W. The value of intracranial pressure monitoring in acute hemispheric stroke. Neurology. 1996;47:393—8.
78. Jensen MB, St Louis EK. Management of acute cerebellar stroke. Arch Neurol. 2005;62:537—44.
79. Bladin CF, Alexandrov AV, Bellavance A, Bornstein N, Chambers B, Cote R, et al. Seizures after stroke: a prospective multicenter study. Arch Neurol. 2000;57:1617—22.
80. Ryvlin P, Montanov A, Nighoghossian N. Optimizing therapy of seizures in stroke patients. Neurology. 2006;67 Suppl 4:S83—9.
81. Kwan J, Wood E. Antiepileptic drugs for the primary and secondary prevention of seizures after stroke. Cochrane Database Syst Rev. 2010;1:CD005398.
82. Kutlu G, Gomceli YB, Unal Y, Inan LE. Levetiracetam monotherapy for late poststroke seizures in the elderly. Epilepsy Behav. 2008;13:542—4.
83. Belcastro V, Pierguidi L, Tambasco N. Levetiracetam in brain ischemia: clinical implications in neuroprotection and prevention of post-stroke epilepsy. Brain Dev. 2011;33:289—93.
84. Aslanyan S, Weir CJ, Diener HC, Kaste M, Lees KR, GAIN International Steering Committee and Investigators. Pneumonia and urinary tract infection after acute ischaemic stroke: a tertiary analysis of the GAIN International trial. Eur J Neurol. 2004;11:49—53.
85. Bath PM, Iddenden R, Bath FJ. Low-molecular-weight heparins and heparinoids in acute ischemic stroke: a meta-analysis of randomized controlled trials. Stroke. 2000;3:1770—8.
86. International Stroke Trial Collaborative Group. The International Stroke Trial (IST): a randomized trial of aspirin, subcutaneous heparin, both or neither among 19435 patients with acute ischaemic stroke. Lancet. 1997;349:1569—81.
87. CAST (Chinese Acute Strke Trial) Collaborative Group. CAST: randomized placebo controlled trial of early aspirin use in 20000 patients with acute ischaemic stroke. Lancet. 1997;349:1641—9.
88. Naccarato M, Chiodo Grandi F, Dennis M, Sandercock PA. Physical methods for preventing deep vein thrombosis in stroke. Cochrane Database Syst Rev. 2010;8:CD001922.
89. Candelario-Jalil E. Injury and repair mechanisms in ischemic stroke: considerations for the development of novel neurotherapeutics. Curr Opin Investig Drugs. 2009;10:644—54.
90. Rodríguez-González R, Hurtado O, Sobrino T, Castillo J. Neuroplasticity and cellular therapy in cerebral infarction. Cerebrovasc Dis. 2007;24 Suppl. 1:S167—80.
91. Burns TC, Verfaillie CM, Low WC. Stem cells for ischemic brain injury: a critical review. J Comp Neurol. 2009;515:125—44.
92. Saxena R, Lewis S, Berge E, Sandercock PA, Koudstaal PJ. Risk of early death and recurrent stroke and effect of heparin in 3169 patients with acute ischemic stroke and atrial fibrillation in the International Stroke Trial. Stroke. 2001;32:2333—7.
93. Cerebral Embolism Study Group. Immediate anticoagulation and embolic stroke. A randomized trial. Stroke. 1983;14:668—76.
94. Cerebral Embolism Study Group. Immediate anticoagulation and embolic stroke. Brain hemorrhage and management options. Stroke. 1984;15:779—89.
95. Rödén-Jüllig A, Britton M. Effectiveness of heparin treatment for progressing ischaemic stroke: before and after study. J Intern Med. 2000;248:287—91.
96. Sandercock PA, Counsell C, Kamal AK. Anticoagulants for acute ischaemic stroke. Cochrane Database Syst Rev. 2008;4:CD000024.
97. Paciaroni M, Agnelli G, Micheli S, Caso V. Efficacy and safety of anticoagulant treatment in acute cardioembolic stroke: a meta-analysis of randomized controlled trials. Stroke. 2007;38:423—30.
98. Kay R, Wong KS, Yu YL, Chan YW, Tsoi TH, Ahuja AT, et al. Low molecular weight heparin for the treatment of acute ischemic stroke. N Engl J Med. 1995;333:1588—93.
99. Hommel M, for the FISS Investigators group. Fraxiparine in Ischemic Stroke Study (FISS bis). Cerebrovasc Dis. 1998;8 Suppl. 4:S1—103.
100. The Publications Committee for the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Investigators. Low molecular weight heparinoid, ORG 10172 (danaparoid), and outcome after acute ischemic stroke: a randomized controlled trial. J Am Med Assoc. 1998;279:1265—72.
101. Berge E, Abdelnoor M, Nakstad PH, Sandset PM. Low molecular-weight heparin versus aspirin in patients with acute ischaemic stroke and atrial fibrillation: a double-blind randomised study. HAEST Study Group. Heparin in Acute Embolic Stroke Trial. Lancet. 2000;355:1205—10.
102. Bath PM, Lindenstrom E, Boysen G, De Deyn P, Friis P, Leys D, et al. Tinzaparin in acute ischaemic stroke (TAIST): a randomised aspirin-controlled trial. Lancet. 2001;358:702—10.
103. Sandercock P, Counsell C, Stobbs S. Low-molecular-weight heparins or heparinoids versus standard unfractionated heparin for acute ischaemic stroke. Cochrane Database Syst Rev. 2005;2:CD000119.
104. Sherman OG, Atkinson RP, Chippeudale T, Levin KA, Ng K, Intrell N, et al. The STAT study: a randomized controlled trial. J Am Med Assoc. 2000;283:2395—403.
105. Orgogozo JM, Verstraete M, Kay R, Hennerici M, Lenzi GL. Outcomes of ancrod in acute ischemic stroke. Independent Data and Safety Monitoring Board for ESTAT. Steering Committee for ESTAT. European stroke treatment with ancrod trial. J Am Med Assoc. 2000;284:1926—7.
106. Zheng MC, Sandercock P, Hong CP, Counsell C, Collins R, Li SL, et al. Indications for early aspirin use in acute ischemic stroke: a combined analysis of 40,000 randomized patients from the Chinese Acute Stroke Trial and the International Stroke Trial. Stroke. 2000;31:1240—9.
107. Morris DC, Silver B, Mitsias P, Lewandowski C, Patel S, Daley S, et al. Treatment of acute stroke with recombinant tissue plasminogen activator and abciximab. Acad Emerg Med. 2003;10:1396—9.
108. Straub S, Junghans U, Jovanovic V, Wittsack HZ, Seitz RJ, Siebler M. Systemic thrombolysis with recombinant tissue plasminogen activator and tirofiban in acute middle cerebral artery occlusion. Stroke. 2004;35:705—9.

109. Abciximab Emergent Stroke Treatment Trial (AbESTT) Investigators. Emergency administration of abciximab for treatment of patients with acute ischemic stroke: results of a randomized phase 2 trial. Stroke. 2005;36:880—90.
110. The Internet Stroke Center. Stroke trials. Available from: http://www.strokecenter.org/trials [accessed 2011].
111. Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, von Kummer R, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The Eurpean Cooperative Acute Stroke Study (ECASS). J Am Med Assoc. 1995;274:1017—25.
112. The National Institute of Neurological Disorders and Stroke rtPA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med. 1995;333: 1581—7.
113. Hacke W, Kaste M, Fieschi C, Von Kummer R, Davalos A, Meier D, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Lancet. 1998;352: 1245—51.
114. Clark WM, Wissman S, Albers GW, Jhamandas JH, Madden KP, Hamilton S. Recombinant tissue-type plasminogen activator (alteplase) for ischemic stroke 3—5 hours after symptom onset. The ATLANTIS study: a randomized controlled trial. J Am Med Assoc. 1999;282:2019—26.
115. Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, et al. Thrombolysis with alteplase 3—4.5 hours after acute ischemic stroke. N Engl J Med. 2008;359:1317—29.
116. Hacke W, Brott T, Caplan L, Meier D, Fieschi C, von Kummer R, et al. Thrombolysis in acute ischemic stroke: controlled trials and clinical experience. Neurology. 1999;53 Suppl. 4:S3—14.
117. Hacke W, Donan G, Fieschi C, Kaste M, von Kummer R, Broderick JP, 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.
118. Wardlaw JM, Murray V, Berge E, sel Zoppo GJ. Thrombolysis for acute ischemic stroke. Cochrane Database Syst Rev. 2009;4. DC:000213.
119. Wahlgren N, Ahmed N, Dávalos A, Ford GA, Grond M, Hacke W, et al. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. Lancet. 2007;369:275—82.
120. Ahmed N, Wahlgren N, Grond M, Hennerici M, Lees KR, Mikulik R, et al. Implementation and outcome of thrombolysis with alteplase 3—4.5 h after an acute stroke: an updated analysis from SITS-ISTR. Lancet Neurol. 2010;9: 866—74.
121. Mishra NK, Ahmed N, Andersen G, Egido JA, Lindsberg PJ, Ringleb PA, et al. Thrombolysis in very elderly people: controlled comparison of SITS International Stroke Thrombolysis Registry and Virtual International Stroke Trials Archive. Br Med J. 2010;341:c6046.
122. Mishra NK, Davis SM, Kaste M, Lees KR, VISTA Collaboration. Comparison of outcomes following thrombolytic therapy among patients with prior stroke and diabetes in the Virtual International Stroke Trials Archive (VISTA). Diabetes Care. 2010;33:2531—7.
123. Selim M, Kumar S, Fink J, Schlaug G, Caplan LR, Linfante I. Seizure at stroke onset: should it be an absolute contraindication to thrombolysis? Cerebrovasc Dis. 2002;14:54—7.
124. De Keyser J, Gdovinová Z, Uyttenboogaart M, Vroomen PC, Luijckx GJ. Intravenous alteplase for stroke: beyond the guidelines and in particular clinical situations. Stroke. 2007;38:2612—8.
125. Alexandrov AV, Grotta JC. Arterial reocclusion in stroke patients treated with intravenous tissue plasminogen activator. Neurology. 2002;59:862—7.
126. Alexandrov AV, Molina CA, Grotta JC, Garami Z, Ford SR, Álvarez-Sabín J, et al. Ultrasound-enhanced systemic thrombolysis for acute ischemic stroke. N Engl J Med. 2004;351:2170—8.
127. Molina CA, Barreto AD, Tsivgoulis G, Sierzenski P, Malkoff MD, Rubiera M, et al. Transcranial ultrasound in clinical sonothrombolysis (TUCSON) trial. Ann Neurol. 2009;66:28—38.
128. Gahn G, Barlinn K, Dzialowski I, Puetz V, Kunz A, Hentschel H, et al. Combined thrombolysis with abciximab and rtPA in patients with middle cerebral artery occlusion. Acta Neurol Scand. 2010;121:63—6.
129. Haley Jr EC, Thompson JL, Grotta JC, Lyden PD, Hemmen TG, Brown DL, et al. Phase IIB/III trial of tenecteplase in acute ischemic stroke: results of a prematurely terminated randomized clinical trial. Stroke. 2010;41:707—11.
130. Parsons MW, Miteff F, Bateman GA, Spratt N, Loiselle A, Attia J. Levi CRAcute ischemic stroke: imaging-guided tenecteplase treatment in an extended time window. Neurology. 2009;72:915—21.
131. Hacke W, Albers G, Al-Rawi Y, Bogousslavsky J, Davalos A, Eliasziw M, et al. The Desmoteplase in Acute Ischemic Stroke Trial (DIAS): a phase II MRI-based 9-hour window acute stroke thrombolysis trial with intravenous desmoteplase. Stroke. 2005;36:66—73.
132. Furlan AJ, Eyding D, Albers GW, Al-Rawi Y, Lees KR, Rowley HA, et al. Dose Escalation of Desmoteplase for Acute Ischemic Stroke (DEDAS): evidence of safety and efficacy 3—9 hours after stroke onset. Stroke. 2006;37:1227—31.
133. Hacke W, Furlan AJ, Al-Rawi Y, Davalos A, Fiebach JB, Gruber F, et al. Intravenous desmoteplase in patients with acute ischaemic stroke selected by MRI perfusion—diffusion weighted imaging or perfusion CT (DIAS-2): a prospective, randomised, double-blind, placebo-controlled study. Lancet Neurol. 2009;8:141—50.
134. Del Zoppo GJ, Higashida RT, Furlan AJ, Pessin MS, Rowley HA, Gent M, the PROACT investigators. (PROACT): a phase II randomized trial of recombinant prourokinase by direct arterial delivery in acute middle cerebral artery stroke. Stroke. 1998;29:4—11.
135. Furlan A, Higashida R, Weschler L, Gent M, Rowley H, Kase C, et al. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. J Am Med Assoc. 1999;282:2003—11.
136. Mattle HP, Arnold M, Georgiadis D, Baumann C, Nedeltchev K, Benninger D, et al. Comparison of intraarterial and intravenous thrombolysis for ischemic stroke with hyperdense middle cerebral artery sign. Stroke. 2008;39:379—83.
137. Lee M, Hong KS, Saver JL. Efficacy of intra-arterial fibrinolysis for acute ischemic stroke: meta-analysis of randomized controlled trials. Stroke. 2010;41:932—7.
138. Meyers PM, Schumacher HC, Higashida RT, Barnwell SL, Creager MA, Gupta R, et al. Indications for the performance of intracranial endovascular neurointerventional procedures: a scientific statement from the American Heart Association. Circulation. 2009;119:2235—49.
139. Lindsberg PJ, Soinne L, Tatlisumak T, Roine RO, Kallela M, Häppölä O, et al. Long-term outcome after intravenous thrombolysis of basilar artery occlusion. J Am Med Assoc. 2004;292:1826—62.
140. Hill MD, Barber PA, Demchuk AM, Newcommon NJ, Cole-Haskayne A, Ryckborst K, et al. Acute intravenous-intra-arterial revascularization therapy for severe ischemic stroke. Stroke. 2002;33:279—82.
141. Zaidat OO, Suarez JI, Santillan C, Sunshine JL, Tarr RW, Paras VH, et al. Response to intra-arterial and combined intravenous and intra-arterial thrombolytic therapy in patients with distal internal carotid artery occlusion. Stroke. 2002;33: 1821—6.

142. IMS Study Investigators. Combined intravenous and intraarterial recanalization for acute ischemic stroke: The Interventional Management of Stroke Study. Stroke. 2004;35: 904—11.
143. IMS III. Interventional management of stroke III; 2011. Available from: http://www.strokecenter.org/trials/trialDetail.aspx?tid=747&search_string=IMS
144. Gobin YP, Starkman S, Duckwiler GR, Grobelny T, Kidwell CS, Jahan R, et al. MERCI 1: a phase 1 study of mechanical embolus removal in cerebral ischemia. Stroke. 2004;35: 2848—54.
145. Smith WS, Sung G, Saver J, Budzik R, Duckwiler G, Liebeskind DS, et al. Mechanical thrombectomy for acute ischemic stroke: final results of the Multi MERCI trial. Stroke. 2008;39: 1205—12.
146. Josephson SA, Saver JL, Smith WS, Merci and Multi Merci Investigators. Comparison of mechanical embolectomy and intraarterial thrombolysis in acute ischemic stroke within the MCA: MERCI and Multi MERCI compared to PROACT II. Neurocrit Care. 2009;10:43—9.
147. Penumbra Pivotal Stroke Trial Investigators. The penumbra pivotal stroke trial: safety and effectiveness of a new generation of mechanical devices for clot removal in intracranial large vessel occlusive disease. Stroke. 2009;40:2761—8.
148. Gutiérrez M, Merino J, Alonso de Leciñana M, Díez-Tejedor E. Cerebral protection, brain repair and cell therapy in ischemic stroke. Cerebrovasc Dis. 2009;27 Suppl. 1:S177—86.
149. Ginsberg MD. Neuroprotection for ischemic stroke: past, present and future. Neuropharmacology. 2008;55:363—89.
150. Fisher M, Feuerstein G, Howells DW, Hurn PD, Kent TA, Savitz SI, et al. Update of the stroke therapy academic industry roundtable preclinical recommendations. Stroke. 2009;40:2244—50.
151. Mohr JP, Orgogozo JM, Harrison MJG, Wahlgren NG, Gelmers JH, Matínez-Vila E, et al. Meta-analysis of oral nimodipine trials in acute ischemic stroke. Cerebrovasc Dis. 1994;4: 197—203.
152. Horn J, Limburg M, Vermeulen M. VENUS-Very Early Nimodipine Use in Stroke: final results from a randomised placebo controlled trial. Cerebrovasc Dis. 1999;9 Suppl. 1:S127.
153. Wahlgren NG, MacMahon DG, DeKeyser J, Indredavik B, Ryman T, for the INWEST Study Group. Intravenous Nimodipine West European Stroke Trial (INWEST) of nimodipine in the treatment of acute ischemic stroke. Cerebrovasc Dis. 1994;4:204—10.
154. Rosenbaum D, Zabranski J, Frey J, Yatsu F, Marler J, Speztler R, et al. Early treatment of ischemic stroke with a calcium antagonist. Stroke. 1991;33:437—41.
155. Oczkowski WJ, Hachinski VC, Bogousslavsky J, Barnett HJM, Carruthers SG. A double blind randomized trial of PY 108-086 in acute ischemic cerebral infarction. Stroke. 1989;20:604—8.
156. Lataste X, Maurer W, Whitehead J, the ASCLEPIOS study group. Application of sequential methods to clinical trial in stroke. The ASCLEPIOS study. In: 2nd World Congress of Stroke. 1992. p. S16.
157. Franke CL, Palm R, Dalby M, Schoonderwaldt HC, Hantson L, Eriksson B, et al. Fllunarizine in nstroke treatment (FIST): a double blind placebo controlled trial in Scandinavia and the Netherlands. Acta Neurol Scand. 1996;93:56—60.
158. Horn J, Limburg M. Calcium antagonists for acute ischemic stroke (cochrane review). In: The Cochrane Library, Issue 3. Oxford: Update software; 2000.
159. Bozik ME, Hommel M, Grotta J, Fisher M, Fayad P, Bogousslavsky J, et al. POST-011: efficacy and safety of maxipost in patients with acute stroke. Cerebrovasc Dis. 2001;11 Suppl. 4:S127.
160. Davis SM, Alberts GW, Diener HC, Lees KR, Norris J. Termination of acute stroke studies involving selfotel treatment (letter). Lancet. 1997;349:32.
161. Albers GW, Atkinson RP, Kelley RE, Rosenbaum MD, on behalf of the Dextrorphan Study Group. Safety, tolerability and pharmacokinetics of the N-methyl-D-aspartate antagonist dextrorphan in patients with acute stroke. Stroke. 1995;26: 254—8.
162. Albers GW, Goldstein LB, Hall D, Lsko LM. Aptiganel hydrochloride in acute ischemic stroke: a randomized controlled trial. J Am Med Assoc. 2001;286:2673—82.
163. Muir KW, Lees KR, Ford I, Davis S. Magnesium for acute stroke (Intravenous Magnesium Efficacy in Stroke trial): randomized controlled trial. Lancet. 2004;363:439—45.
164. Lees KR, Asplund K, Carolei A, Davis SM, Dienet HC, Kaste M, et al. Glycine antagonist (gavastinel) in neuroprotection (GAIN International) in patients with acute stroke: a randomised controlled trial. Lancet. 2000;355:1949—54.
165. Sacco RL, de Rosa JT, Haley Jr EC, Levin B, Ordronneau P, Phillips SJ, et al. Glycine antagonist in neuroprotection for patients with acute stroke: GAIN Americas: a randomized controlled trial. J Am Med Assoc. 2001;285: 1719—28.
166. Grotta J. Lubeluzole treatment of acute ischemic stroke. The US and Canadian Lubeluzole Ischemic Stroke Study Group. Stroke. 1997;28:2338—46.
167. Diener HC. Multinational randomized controlled trial of lubeluzole in acute ischemic stroke. European and Australian Lubeluzole Ischemic Stroke Study Group. Cerebrovasc Dis. 1998;8:172—81.
168. Wahlgren NG, Ranasinha KW, Rosolacci T, Franke CL, van Erven PM, Ashwood T, et al. Clomethiazole acute stroke study (CLASS): results of a randomized, controlled trial of clomethiazole versus placebo in 1360 acute stroke patients. Stroke. 1999;30:21—8.
169. Lyden P, Shuaib A, Ng K, Levin K, Atkinson RP, Rajput A, et al. Clomethiazole Acute Stroke Study in ischemic stroke (CLASS-I): final results. Stroke. 2002;33:122—8.
170. Lyden P, Jacoby M, Schim J, Albers G, Mazzeo P, Ashwood T, et al. The Clomethiazole Acute Stroke Study in tissue-type plasminogen activator-treated stroke (CLASS-T): final results. Neurology. 2001;57:1199—205.
171. Lodder J, van Raak L, Hilton A, Hardy E, Kessels A, EGASIS Study Group. Diazepam to improve acute stroke outcome: results of the early GABA-Ergic activation study in stroke trial. A randomized double-blind placebo-controlled trial. Cerebrovasc Dis. 2006;21:120—7.
172. Clark WM, Raps EC, Tong DC, Kelly RE. Cervene (Nalmefene) in acute ischemic stroke: final results of a phase III efficacy study. The Cervene Stroke Study Investigators. Stroke. 2000;31:1234—9.
173. Peters GR, Hwang LJ, Musch B, Brosse DM, Orgogozo JM. Safety and efficacy of 6 mg/kg/day tirilazad mesylate in patients with acute ischemic stroke (TESS study). Stroke. 1996;27: 195.
174. The RANTTAS Investigators. A randomized trial of tirilazad mesylate in patients with acute stroke (RANTTAS). Stroke. 1996;27:1453—8.
175. Haley EC, on behalf of the RANTTAS Investigators II. High dose tirilazad mesylate in patients with acute stroke (RANTTAS II). Stroke. 1998;29:1256—7.
176. Tirilazad International Steering Committee. Tirilazad Mesylate in acute ischemic stroke: a systematic review. Stroke. 2000;31:2257—65.
177. Yamaguchi T, Sano K, Takakura K, Saito I, Shinohara Y, Asano T, et al. Ebselen in acute ischemic stroke: a placebo-controlled, double-blind clinical trial. Stroke. 1998;29:12—7.
178. Edaravone Acute Infarction Study. Effect of a novel free radical scavenger, edaravone (MCI-186) on acute brain infarction. Randomized placebo-controlled double-blind study at multicenters. Cerebrovasc Dis. 2003;15:222—9.

179. Lees KR, Zivin JA, Ashwood T, Davalos A, Davis SM, Diener HC, et al. NXY-059 for acute ischemic stroke. N Engl J Med. 2006;354:588—600.
180. Shuaib A, Lees KR, Lyden P, Grotta J, Davalos A, Davis SM, et al. NXY-059 for the treatment of acute ischemic stroke. N Engl J Med. 2007;357:562—71.
181. Enlimomab Acute Stroke Trial Investigators. Use of anti-ICAM-1 therapy in ischemic stroke: results of the Enlimomab Acute Stroke Trial. Neurology. 2001;57:1428—34.
182. Krams M, Lees KR, Hacke W, Grieve AP, Orgogozo JM, Ford GA, ASTIN Study Investigators. Acute Stroke Therapy by Inhibition of Neutrophils (ASTIN): an adaptive dose-response study of UK-279,276 in acute ischemic stroke. Stroke. 2003;34:2543—8.
183. D'Orlando JK, Sandgadge BW. Citicoline (CDP-Choline): mechanisms of action and effects on ischemic brain injury. Neurol Res. 1995;17:281—4.
184. Clark WM, Warach SJ, Pettigrew LC, Gammans RE, Sabounjian LA, for the Citicoline Stroke Study Group. A randomized dose-response trial of citicoline in acute ischemic stroke patients. Neurology. 1997;49:671—8.
185. Clark WM, Williams BJ, Selzer KA, Zweifler RM, Sabounjian LA, Gammans RE. A randomized efficacy trial of citicoline in patients with acute ischemic stroke. Stroke. 1999;30:2592—7.
186. Clark WM, Wechsler LR, Sabounjian LA, Schwiderski UE, for the Citicoline Stroke Study Group. A phase III randomized efficacy trial of 2000 mg citicoline in acute ischemic stroke patients. Neurology. 2001;57:1595—602.
187. Warach S, Pettigrew LC, Dashe JF, Pullicino P, Lefkowitz DM, Sabounjian LA, et al. Effect of citicoline on ischemic lesions as measured by diffusion-weighted magnetic resonance imaging. Citicoline 010 Investigators. Ann Neurol. 2000;48:713—22.
188. Dávalos A, Castillo J, Álvarez-Sabín J, Secades JJ, Mercadal J, López S, et al. Oral citicoline in acute ischemic stroke: an individual patient data pooling analysis of clinical trials. Stroke. 2002;33:2850—7.
189. Dávalos A, Secades J. Citicoline preclinical and clinical update 2009—2010. Stroke. 2011;42 Suppl.:S36—9.
190. De Deyn PP, Reuck JD, Deberdt W, Vlietinck R, Orgogozo JM. Treatment of acute ischemic stroke with piracetam. Members of the Piracetam in Acute Stroke Study (PASS) Group. Stroke. 1997;28:2347—52.
191. Bogousslavsky J, Victor SJ, Salinas EO, Pallay A, Donnan GA, Fieschi C, et al. Fiblast (trafermin) in acute stroke: results of the European—Australian phase II/III safety and efficacy trial. Cerebrovasc Dis. 2002;14:239—51.
192. Candelise L, Ciccone A. Gangliosides for acute ischemic stroke. Cochrane Database Syst Rev. 2001:CD000094.
193. Hong Z, Moessler H, Bornstein N, Brainin M, Heiss WD, CASTA-investigators. A double-blind, placebo-controlled, randomized trial to evaluate the safety and efficacy of Cerebrolysin in patients with acute ischaemic stroke in Asia-CASTA. Int J Stroke. 2009;4:406—12.
194. Jianu DC, Muresanu DF, Bajenaru O, Popescu BO, Deme SM, Moessler H, et al. Cerebrolysin adjuvant treatment in Broca's aphasics following first acute ischemic stroke of the left middle cerebral artery. J Med Life. 2010;3:297—307.
195. Ziganshina LE, Abakumova T, Kuchaeva A. Cerebrolysin for acute ischaemic stroke. Cochrane Database Syst Rev. 2010;4:CD007026.
196. Scandinavian Stroke Study Group. Multicenter Trial of hemodilution in acute ischemic stroke. I. Results in the total patient population. Stroke. 1987;18:691—9.
197. Italian Acute Stroke Study Group. Haemodilution in acute stroke: results of the Italian haemodilution trial. Lancet. 1988;1:318—21.
198. Goslinga H, Eijzenbach V, Heuvelmans JH, Van der Laan de Vries E, Melis VM, Schmid-Schönbein H, et al. Custom-tailored hemodilution with albumin and crystalloids in acute ischemic stroke. Stroke. 1992;23:181—8.
199. Palesch YY, Hill MD, Ryckborst KJ, Tamariz D, Ginsberg MD. The ALIAS Pilot Trial: a dose-escalation and safety study of albumin therapy for acute ischemic stroke II: neurologic outcome and efficacy analysis. Stroke. 2006;37:2107—14.
200. Ginsberg MD, Palesch YY, Hill MD. The ALIAS (ALbumin In Acute Stroke) phase III randomized multicentre clinical trial: design and progress report. Biochem Soc Trans. 2006;34:1323—6.
201. Lampl Y, Boaz M, Gilad R, Lorberboym M, Dabby R, Rapoport A, et al. Minocycline treatment in acute stroke: an open-label, evaluator-blinded study. Neurology. 2007;69:1404—10.
202. Martí-Fàbregas J, Gomis M, Arboix A, Aleu A, Pagonabarraga J, Belvís R, et al. Favorable outcome of ischemic stroke in patients pretreated with statins. Stroke. 2004;35:1117—21.
203. Fuentes B, Martínez-Sánchez P, Díez-Tejedor E. Lipid-lowering drugs in ischemic stroke prevention and their influence on acute stroke outcome. Cerebrovasc Dis. 2009;27 Suppl. 1:S126—33.
204. Martínez-Sánchez P, Rivera-Ordóñez C, Fuentes B, Ortega-Casarrubios MA, Idrovo L, Díez-Tejedor E. The beneficial effect of statins treatment by stroke subtype. Eur J Neurol. 2009;16:127—33.
205. Blanco M, Nombela F, Castellanos M, Rodríguez-Yáñez M, García-Gil M, Leira R, et al. Statin treatment withdrawal in ischemic stroke: a controlled randomized study. Neurology. 2007;69:904—10.
206. Biffi A, Devan WJ, Anderson CD, Cortellini L, Furie KL, Rosand J, et al. Statin treatment and functional outcome after ischemic stroke: case-control and meta-analysis. Stroke. 2011;42:1314—9.
207. Gutiérrez M, Merino JJ, Alonso de Leciñana M, Díez-Tejedor E. Cerebral protection, brain repair, plasticity and cell therapy in ischemic stroke. Cerebrovasc Dis. 2009;27 Suppl. 1:S177—86.
208. Ehrenreich H, Weissenborn K, Prange H, Schneider D, Weimar C, Wartenberg K, et al. Recombinant human erythropoietin in the treatment of acute ischemic stroke. Stroke. 2009;40:e647—56.
209. Gutiérrez-Fernández M, Rodríguez-Frutos B, Álvarez-Grech J, Vallejo-Cremades MT, Expósito-Alcaide M, Merino J, et al. Functional recovery after hematic administration of allogenic mesenchymal stem cells in acute ischemic stroke in rats. Neuroscience. 2011;175:394—405.
210. Lee JS, Hong JM, Moon GJ, Lee PH, Ahn YH, Bang OY, et al. A long-term follow-up study of intravenous autologous mesenchymal stem cell transplantation in patients with ischemic stroke. Stem Cells. 2010;28:1099—106.
211. Suárez-Monteagudo C, Hernández-Ramírez P, Álvarez-González L, García-Maeso I, de la Cuétara-Bernal K, Castillo-Díaz L, et al. Autologous bone marrow stem cell neurotransplantation in stroke patients. An open study. Restor Neurol Neurosci. 2009;27:151—61.
212. Guenther G, Arauz A. Cerebral venous thrombosis: a diagnostic and treatment update. Neurologia. 2011;26:488—98.
213. Bousser MG, Ferro JM. Cerebral venous thrombosis: an update. Lancet Neurol. 2007;56:162—70.
214. Saposnik G, Barinagarrementeria F, Brown Jr RD, Bushnell CD, Cucchiara B, Cushman M, et al. Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2011;42:1158—92.
215. Einhäupl KM, Villringer A, Meister W. Heparin treatment in sinus venous treatment thrombosis. Lancet. 1991;338:597—600.
216. De Bruijn FTM, Stam J, para el Cerebral Venous Sinus Thrombosis Study Group. Randomized, placebo-controlled trial of

anticoagulant treatment with low-molecular-weight heparin for cerebral sinus thrombosis. Stroke. 1999;30:484—8.
217. Stam J, De Bruijn SF, DeVeber G. Anticoagulation for cerebral sinus thrombosis. Cochrane Database Syst Rev. 2002;4:CD002005.
218. Coutinho JM, Ferro JM, Canhão P, Barinagarrementeria F, Bousser MG, Stam J, ISCVT Investigators. Unfractionated or low-molecular weight heparin for the treatment of cerebral venous thrombosis. Stroke. 2010;41:2575—80.
219. Canhão P, Falcão F, Ferro JM. Thrombolytics for cerebral sinus thrombosis: a systematic review. Cerebrovasc Dis. 2003;15:159—66.
220. Ferro JM, Crassard I, Coutinho JM, Canhão P, Barinagarrementeria F, Cucchiara B, et al. Decompressive surgery in cerebrovenous thrombosis. A multicentre registry and a systematic review of individual patient data. Stroke. 2011;42:2825—31.