MEDICAL MANAGEMENT OF STROKE

Keith W Muir

i12

Management of stroke has been revolutionised over the past decade, and therapeutic nihilism is no longer justified. The advent of acute treatments, especially thrombolysis, where the window of opportunity for intervention is very short and the treatment carries risk, emphasises the paramount importance of correct clinical diagnosis. Neurologists will need to adopt a front line role that is unfamiliar in the UK if therapeutic advances are to be implemented safely. Closer involvement in stroke care also necessitates that neurologists keep abreast of developments in cardiovascular medicine: vascular neurologists require to be both electrician and plumber.

CLINICAL DIAGNOSIS

Misdiagnosis of stroke is common: 20% of emergency department diagnoses may be incorrect, and 10% of stroke unit patients are discharged with an alternative diagnosis. Many common misdiagnoses are characterised by global rather than focal cerebral dysfunction (sepsis, hypoglycaemia, drug overdose, and metabolic disturbance all being common). These problems attest to major and basic deficits in public and non-specialist medical knowledge of the characteristics of stroke. Many misdiagnoses are serious and treatable conditions. Some common neurological differential diagnoses require prompt treatment (for example, seizure, brain tumour, subdural haematoma) while more benign conditions (for example, Bell's palsy, peripheral nerve pressure palsies) are important largely in order to avoid unnecessary treatment. Uncommon neurological disorders often cause diagnostic difficulty to non-neurologists: for example, when faced with "progressing brainstem stroke" it is wise to consider Miller Fisher syndrome or myasthenia gravis.

Pertinent features of the clinical examination are usefully summarised by the test items included in the US National Institutes of Health stroke scale (see box below), and a syndromic classification derived from the Oxfordshire community stroke project (OCSP) is clinically useful with respect to aetiology and prognosis (table 1). However, the accuracy of OCSP classification is limited in the first 24 hours after onset, and diffusion weighted magnetic resonance (MR) imaging is redefining localisation of strokes.

Clinical features cannot distinguish ischaemic stroke from intracerebral haemorrhage (ICH). Scoring systems to improve diagnosis (for example, Guy's, Siriraj) perform poorly when applied to datasets other than that from which they were derived. Imaging is essential to make this distinction (see accompanying article by Wardlaw, p i7).

Where to treat

Most patients should be sent to hospital to ascertain clinical and radiological diagnosis, and to permit specific acute treatments that reduce mortality and improve functional outcome. There is now good evidence from a randomised, controlled trial that inpatient care in a geographically discrete stroke unit is superior to domiciliary or supported general medical ward care with respect to survival and disability.

Patients with transient ischaemic attacks and non-disabling stroke can usually be seen as outpatients provided assessment can be conducted promptly. Domestic circumstances and comorbidities influence the decision. Some patients with frequent transient ischaemic attacks require hospitalisation for stabilisation and investigation.

Table 1 Oxfordshire community stroke project classification

► TACS	Total anterior circulation syndrome	Hemianopia, hemiparesis, and higher cortical dysfunction
► PACS	Partial anterior circulation syndrome	Any two of TACS criteria or isolated higher cortical dysfunction
► LACS	Lacunar syndrome	Pure motor, pure sensory, sensorimotor strokes, clumsy hand-dysarthria syndrome or ataxic hemiparesis
► POCS	Posterior circulation syndrome	Isolated hemianopia or brainstem or cerebellar signs

Correspondence to: Dr Keith W Muir, Institute of Neurological Sciences, Southern General Hospital, Glasgow G51 4TF, UK. k.muir@clinmed.gla.ac.uk

National Institutes of Health stroke scale test items: a useful summary of relevant features in acute stroke

- ▶ Level of consciousness
 - questions
 - commands
- ▶ Facial weakness
- ▶ Upper limb weakness
- ▶ Lower limb weakness
- ▶ Sensory loss
- ▶ Conjugate eye deviation
- ▶ Visual fields
- ▶ Extinction or inattention (sensory or visual inattention)
- ▶ Ataxia
- ▶ Dysarthria
- ▶ Dysphasia

Acute treatment

Ischaemic stroke

“Time is brain”—following middle cerebral artery (MCA) occlusion, irreversible ischaemic brain damage evolves over hours. Reperfusion can rescue tissue which is functionally inactive but still viable (the “ischaemic penumbra”). Animal studies suggest other possible interventions that may also salvage the penumbra.

Thrombolysis

Thrombolytic drug treatment for stroke is established in North America, and, although not yet licensed, in stroke centres throughout Europe, South Asia, and Australasia. Intravenous recombinant tissue plasminogen activator (rt-PA) in a dose of 0.9 mg/kg (maximum 90 mg) given over one hour has been licensed in the USA since 1996 for use within three hours of onset of ischaemic stroke. Evidence of efficacy derives from five moderately large randomised controlled trials (fig 1),^{1,2} of which the pivotal NINDS rt-PA trial showed a highly significant increase in the proportion of patients making full neurological recovery from stroke (12% absolute risk reduction, equating to one extra patient fully recovered for every eight treated) with no increase in mortality.¹ In contrast, streptokinase was associated with significant increases in early mortality in three trials; further use of this drug was abandoned on safety grounds, despite a trend towards reduced disability in survivors. The NINDS trial treated uniquely early—half its patients were treated within 90 minutes of onset, half between 91–180 minutes. Three other trials with longer time windows (to a maximum of six hours) have initiated treatment on average 4.5 hours after onset, and have had equivocal results, some of which are attributable to the vagaries of stroke trial design and end

points. Both ECASS trials would have been “positive” with very minor differences in the selection of primary end points.² The small PROACT II trial found significant benefit up to six hours after onset with intra-arterial prourokinase in the highly selected population with angiographically proven proximal MCA occlusion.³

Trial acronyms

ATLANTIS: Alteplase ThromboLysis for Acute Noninterventional Therapy in Ischemic Stroke
 CAST: Chinese Acute Stroke Trial
 ECASS: European Cooperative Acute Stroke Study
 FOOD: Feed Or Ordinary Diet
 GIST: Glucose Insulin in Stroke Trial
 HOPE: Heart Outcomes Prevention Evaluation
 IST: International Stroke Trial
 MAST-I: Multicentre Acute Stroke Trial—Italy
 NASCET: North American Symptomatic Carotid Endarterectomy Trial
 NINDS: National Institutes of Neurological Disorders and Stroke
 PROACT: Prolyse in Acute Cerebral Thromboembolism
 PROGRESS: Perindopril Protection Against Recurrent Stroke Study
 STAT: Stroke Treatment with Ancrod Trial
 STICH: Surgical Treatment of Intracerebral Haemorrhage
 4S: Scandinavian Simvastatin Survival Study

Many questions remain regarding optimal use of rt-PA, but post-licensing experience in the USA, Canada, and Europe suggests that safety and efficacy results matching the original trial can be achieved in routine clinical practice provided that the NINDS protocol is adhered to. Service organisation remains a major barrier to wide implementation of rt-PA, and fewer than 5% of strokes are treated even in enthusiastic US centres.

Intra-arterial thrombolysis has been advocated for basilar artery occlusion. This syndrome is rare, difficult to recognise clinically until advanced, and carries a mortality as high as 90% untreated. Non-randomised studies suggest reduced mortality and morbidity with successful basilar recanalisation.

Antiplatelet drugs

Combined data from three trials involving over 40 000 patients (IST, CAST, and MAST-I)⁴ indicate that initiation of aspirin 150–300 mg within 48 hours of stroke:

- ▶ prevents early recurrent ischaemic stroke (absolute risk reduction 0.7%);
- ▶ reduces death and disability at 3–6 months (1.3%);

Figure 1 Overview of recent trials of intravenous rt-PA thrombolysis using the end point of complete or near complete functional recovery (modified Rankin score of 0–1). Trial acronyms are detailed in the accompanying box. OR, odds ratio; 95% CI, 95% confidence intervals.

- ▶ and (on post-hoc analysis) increases the proportion of patients making a full functional recovery (1.1%);
- ▶ at the expense of a small increase in intracranial (0.2%) and extracranial (0.4%) haemorrhage risk;
- ▶ and with no significant heterogeneity of these effects across any subgroup including intracerebral haemorrhage patients randomised before computed tomography (CT).

Institution of aspirin may therefore be safe where CT is not available. The modest benefit of aspirin is not time dependent within 48 hours, and effects almost certainly reflect early secondary prevention rather than any influence over the acute pathophysiology of stroke.

Other antiplatelet agents have not been subjected to large scale investigation in the acute phase.

Ancrod

Treatment within three hours with ancrod, a snake venom derivative that reduces serum fibrinogen concentrations, significantly increased the proportion of patients making full neurological recovery in a randomised, controlled trial (STAT).⁵ A similar European trial (ESTAT) with a six hour treatment window found no benefit. The magnitude of benefit was less than that of rt-PA in the NINDS trial, and administration was considerably more complex since dose adjustment by fibrinogen concentration is necessary over five days.

Heparin

No significant reduction in death or disability after stroke has been found in any trial of heparin, either as conventional unfractionated (mostly patients in the IST study) or low molecular weight preparations commenced within 24–48 hours after stroke onset, even in subgroups such as patients with atrial fibrillation.⁶ Reduced incidence of recurrent ischaemic stroke and venous thromboembolism are accompanied by increased risk of major intracranial and extracranial bleeding complications. The incidence of clinical venous thromboembolic disease in the acute phase of stroke is low, and the overall risk:benefit ratio is not generally felt to favour routine acute heparin use. Whether safety may be improved by careful monitoring of coagulation indices remains the subject of debate, and two ongoing trials continue to assess potential efficacy in the subgroup of “progressing strokes”. Deferred use of heparin for thromboembolism prophylaxis in immobile patients has not been subjected to randomised, controlled trials to date, but is widely practised.

Neuroprotection

Significant limitation of infarct size is possible in animal models but no clinical benefit has yet been found for several neuroprotective agents in moderately large phase III trials.⁷ Major deficiencies in drug development suggest that the neuroprotection hypothesis has not yet been tested adequately, and several trials are in progress. Trial data indicate potential harm from some putative neuroprotectants, notably nimodipine, corticosteroids, and some NMDA (*N*-methyl-D-aspartate) antagonists.

Stroke units

Systematic review of randomised, controlled trials indicates that organised stroke care reduces mortality and increases the proportion of patients making full functional recovery after stroke.^{8,9} Since trials were conducted in widely differing settings, considerable uncertainty remains over the optimal model for stroke unit care. The UK focus has been on stroke rehabilitation since this was common to all stroke units in

trials. Care is optimally based in a geographically discrete inpatient unit with specialist staff.

Data also suggest strongly that stroke units influence the acute pathophysiology of stroke. The stroke unit trialists’ collaboration found divergence of mortality between stroke and general medical groups within 72 hours of admission, implying a predominant reduction in neurological deaths.⁸ Physiological variables—notably high body temperature, low diastolic blood pressure, and high blood glucose—have detrimental effects on clinical (and experimental) stroke outcome, and a feature of stroke units that provide acute care is protocol driven interventions to correct these and similar variables in the first 24–48 hours. The Trondheim trial found discharge by six weeks to be determined by early mobilisation of patients (average time to mobilisation was eight hours) and use of intravenous fluids to prevent any fall in diastolic blood pressure over the first 24 hours. In this trial, stroke unit patients received less physical and occupational therapy input than those randomised to general medical care. The use of intensive physiological monitoring protocols in the acute phase of stroke is subject to clinical trials at present. A trial of glucose–potassium–insulin treatment to normalise blood glucose in the acute phase of stroke is ongoing (GIST). There are no trial data at present to support the “intensive care” approach adopted by some European countries.

Neurosurgery

Surgical intervention is undertaken when there is raised intracranial pressure likely to prove fatal after ischaemic stroke, usually 3–5 days after onset when cerebral oedema is maximal. Hemicraniectomy has been advocated for “malignant MCA occlusion” syndrome, which is associated with persisting vessel occlusion, and posterior fossa craniectomy with infarct evacuation for cerebellar infarcts. Neither approach yet has the backing of trial evidence, and, while there is no doubt that these procedures are often life saving, there are concerns regarding the disability of survivors.

Intracerebral haemorrhage

There are no good data on the optimal management of ICH. Experimental and clinical data have failed to support the existence of an ischaemic penumbra around the condition, and there is therefore no rationale for neuroprotective drugs. Experimental evidence favours the potential benefit of reducing the volume of clot present, but individual neurosurgical practice varies widely. Clinical trials to date have been few and too small. An ongoing trial (STICH) seeks to determine whether benefit accrues from surgical evacuation of haematoma. Alternative approaches such as haematoma thrombolysis via stereotactically placed catheter have been reported.

Further medical aspects of ICH management have been poorly studied. Patients with ICH derived considerable benefit from stroke unit treatment. Stopping antiplatelet and anticoagulant drugs in the acute phase is routine, but stopping aspirin may have little impact. It is unknown whether drug withdrawal should be lifelong. Since 50% of patients presenting with ICH will go on to have ischaemic stroke, there may be a benefit to resumption of antiplatelet drugs. Although hypertension commonly underlies ICH, some studies report a high incidence of underlying arteriovenous malformation or saccular aneurysms on angiography, and it is not known how extensively ICH patients should be investigated. In older patients, lobar haematomas may signify underlying cerebral amyloid

angiopathy, a condition that confers a significant risk of future ICH and that is associated with dementia. There are no specific therapeutic implications at present.

Venous infarction

Cerebral venous sinus thrombosis (CVST) may present as stroke, but has a broad clinical spectrum, from chronic idiopathic intracranial hypertension to acute life threatening occlusion of the deep venous drainage. Clinical suspicion may be aroused by a more gradual evolution than is typical of arterial stroke, a prominent history of seizures, occurrence in pregnancy or the puerperium, personal or family history of venous thromboembolism or thrombophilia, or imaging features such as lobar haematoma or cortical haemorrhagic infarction. Thrombus within major dural sinuses or the deep venous system is identifiable on MR imaging and MR venography, but cortical vein thromboses are difficult to diagnose because of variability in the normal venous anatomy, and stroke caused by cortical vein thrombosis may be under-recognised.

Only two randomised, controlled trials have been conducted, involving a total of 80 patients. One suggested improved outcome of CVST with intravenous heparin infusion, the other found no benefit from subcutaneous low molecular weight heparin.¹⁰ The great variability in the natural history of CVST, in particular noting that most patients had favourable outcome in the placebo arm of the trials, ensures that there are no good data on which to base a management decision. While heparin appears to be safe, even in patients with haemorrhage, it is unclear whether it is necessary for the majority of patients. Subsequent duration and intensity of anticoagulation with warfarin has not been addressed. The potential of antiplatelet agents, which appear to have an effect on peripheral thromboembolic disease, remains unknown. Enthusiastic centres have reported the use of endovascular thrombolysis with several agents, especially urokinase, but indications for this invasive and potentially dangerous therapeutic modality are not yet established.

In the absence of evidence, expert opinion has generally adopted the approach that heparin should be used for patients with focal central nervous system (CNS) symptoms, especially if there is evidence of progression, or radiological evidence of involvement of the deep venous system, and that thrombolysis should be reserved for patients with progressive CNS symptoms or coma despite heparin. If CVST is complicated by intracranial hypertension, especially with papilloedema and retinal haemorrhages, repeated lumbar puncture may be required to preserve vision, and heparin and anticoagulants must be avoided. If there are compelling clinical grounds for use of anticoagulants in these patients, consideration should be given to alternative means of lowering intracranial pressure such as lumboperitoneal shunting, but this may be equally fraught.

Prevention of secondary complications

Although most deaths within seven days of stroke are attributable to neurological deterioration, recurrent stroke or the development of a mass effect sufficient to compromise consciousness are uncommon. The inadequate generic label "extension of infarction" is often applied loosely to any patient with altered consciousness. Many potentially fatal complications are treatable, and it is necessary to seek reversible causes and consider the clinical and radiological characteristics of the stroke before concluding that deterioration has a neurological basis.

Infection may be present even on hospital admission, commonly pneumonia consequent to hypostasis or aspiration. Hypoxaemia may be deleterious to the cerebral

injury (as may pyrexia) as well as complicating neurological evaluation, and frequently contributes to encephalopathy.

Swallowing is compromised in at least 45% of stroke patients admitted to hospital acutely, increasing the risk of aspiration pneumonia and inadequate hydration and nutrition. The presence or absence of a gag reflex is not indicative of swallowing safety, and standardised bedside assessment is needed (usually a combination of clinical evaluation of vocal quality and water swallowing). Most dysphagia is transient: only 2% of stroke survivors are still dysphagic one month later. Optimal management of persistently impaired swallowing is not established and is presently subject to a randomised, controlled trial (FOOD).

Thromboembolism is rare in the early weeks after stroke (clinical deep vein thrombosis (DVT) incidence around 1% in the first week, although higher if radiologically rather than clinically defined). Early mobilisation, antiplatelet drugs, and rehydration all contribute to prevention. Heparin notably reduces the incidence of DVT and pulmonary thromboembolism, but is associated with higher risk of systemic haemorrhage. Evidence of the effectiveness of physical means of DVT prevention in stroke patients such as graded compression stockings is limited and inconclusive, although stockings are widely used and have few contraindications.

Mechanical problems are common, especially shoulder subluxation, and may contribute to pain and difficulty in mobilising. Early investigation may assist management.

Depression and related **neuropsychiatric** complications are common after stroke (about 50% incidence), including emotional lability ("emotional incontinence"). These are partly a biological response to brain injury, but cannot be localised anatomically. Depression and emotional lability respond to tricyclic antidepressants or selective serotonin reuptake inhibitors.

Seizures complicate 2% of strokes at onset: half are generalised and half focal. They are not of prognostic significance. Overall 3% of ischaemic stroke patients have single, and 3% recurrent, seizures. Risk is higher in patients with large MCA infarcts, and ICH, each of which groups have around a 10% risk of recurrent seizures. Conventional anticonvulsant treatment is usually initiated for recurrent events.

Secondary prevention

There are a number of secondary preventative treatments that must be considered after stroke. There is evidence to support the following treatments:

- ▶ **Antiplatelet treatment**—There is substantial evidence supporting the value of aspirin 75–300 mg. There is no evidence of additional benefit from higher doses. Aspirin plus modified release dipyridamole (200 mg twice daily) or clopidogrel monotherapy (75 mg daily) are more effective, but in the UK cost constraints restrict usage to high risk patients.
- ▶ **Anticoagulation**—Warfarin significantly reduces risk of recurrent stroke, myocardial infarction, and systemic embolism in patients in atrial fibrillation after minor stroke. The risk of recurrence untreated is high (12% per year), and is reduced to 5% by warfarin (number needed to treat 18).
- ▶ **Carotid endarterectomy (CEA)**—CEA greatly reduces recurrent ipsilateral ischaemic stroke risk, with greatest benefit in those with symptomatic stenosis of 70% or greater (NASCET criteria). Carotid stenosis potentially

benefiting from CEA is present in only 8% of patients. Further analyses of NSACET and ECST¹¹ data are ongoing to seek subgroups in whom CEA may be most effective.

- ▶ **Antihypertensive treatment**—Reduction in stroke risk with antihypertensive treatment is probably similar to the relative risk reduction achievable with this therapy in the primary prevention setting. British Hypertension Society guidelines should be adhered to.
- ▶ **ACE inhibition**—The angiotensin converting enzyme (ACE) inhibitor ramipril significantly reduces the risk of stroke and acute coronary syndromes in patients with vascular disease and at least one recognised risk factor, irrespective of blood pressure and other treatments (HOPE trial). Further evidence of ACE inhibitor efficacy in stroke prevention is imminent from the PROGRESS trial.
- ▶ **Statins**—Pravastatin significantly reduces the incidence of stroke and other vascular end points in patients with a history of ischaemic heart disease, irrespective of initial cholesterol concentrations, and possibly independent of cholesterol lowering. Simvastatin exhibits similar effects but is unlicensed in the UK for stroke prevention since this was not a pre-specified end point in the 4S trial. Further trials with statins in stroke patients are ongoing.
- ▶ **Smoking cessation**—Stopping smoking has not been subjected to clinical trials but should be beneficial.

Timing of secondary preventative treatment initiation depends upon the clinical scenario. In minor stroke, most secondary preventative measures can be initiated almost immediately after presentation, although there are potential reasons to defer antihypertensive drugs. In atrial fibrillation, optimal timing of anticoagulation is not known. There is a high risk of spontaneous radiologically defined intracerebral bleeding in large MCA infarcts; in this group it may therefore be prudent to defer anticoagulation in favour of aspirin until an arbitrary “later” stage unless there are compelling individual reasons to expect a very high risk of early recurrence. It is worth remembering that early recurrence of stroke is uncommon (around 2% in the first 14 days), even in atrial fibrillation. In non-disabling strokes, there is probably no need for delay. Patients with poor functional recovery or major comorbidities were excluded from most clinical trials, particularly those of CEA and anticoagulation, and management is generally dictated by individual considerations.

There are no established evidence based guidelines for the secondary prevention of either ICH or CVST. Lowering blood pressure and attendance to general cardiovascular risk factors is appropriate for both. Whether avoidance of antiplatelet agents is necessary or desirable for ICH patients is unknown, but, as noted, these patients have an equally great chance of suffering a future ischaemic event. Genetic and functional screening for inherited thrombophilias is worthwhile in CVST, although this generally informs decisions about risk of peripheral rather than recurrent CVST. This may extend to testing of family members.

Avoidance of oestrogen containing oral contraceptives in women and smoking cessation are also advisable.

References

- 1 **The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group.** Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995;**333**:1581–7.
- ▶ **Definitive trial of intravenous rt-PA thrombolysis given within three hours of stroke onset.**
- 2 **Hacke W, Kaste M, Fieschi C, et al.** Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian acute stroke study Investigators. *Lancet* 1998;**352**:1245–51.
- ▶ **Large trial of rt-PA thrombolysis given within six hours of onset, negative for the chosen primary end point, but positive in favour of rt-PA if a different end point had been selected.**
- 3 **Furlan A, Higashida R, Wechsler L, et al.** Intra-arterial prourokinase for acute ischaemic stroke. The PROACT II study: a randomized controlled trial. Prolase in acute cerebral thromboembolism. *JAMA* 1999;**282**:2003–11.
- ▶ **Trial of intra-arterial thrombolysis for proximal MCA occlusion.**
- 4 **Chen ZM, Sandercock P, Pan HC, 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. On behalf of the CAST and IST collaborative groups. *Stroke* 2000;**31**:1240–9.
- ▶ **Meta-analysis of the combined IST and CAST trials looking at aspirin given within 24–48 hours of acute stroke.**
- 5 **Sherman DG, Atkinson RP, Chippendale T, et al.** Intravenous aniclod for treatment of acute ischemic stroke: the STAT study: a randomized controlled trial. Stroke treatment with aniclod trial. *JAMA* 2000;**283**:2395–403.
- ▶ **The first unequivocally positive trial of a non-thrombolytic treatment for stroke.**
- 6 **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;**31**:1770–8.
- ▶ **Meta-analysis of low molecular weight heparins in acute stroke treatment.**
- 7 **Lees KR, Asplund K, Carolei A, et al.** Glycine antagonist (gavestinel) in neuroprotection (GAIN international) in patients with acute stroke: a randomised controlled trial. GAIN international investigators. *Lancet* 2000;**355**:1949–54.
- ▶ **The largest neuroprotective trial to date—unfortunately with negative results.**
- 8 **Stroke Unit Trialists' Collaboration.** Collaborative systematic review of the randomised trials of organised inpatient (stroke unit) care after stroke. Stroke unit trialists' collaboration. *BMJ* 1997;**314**:1151–9.
- ▶ **The most recent systematic review of 19 trials of organised stroke care, demonstrating clear improvements in outcome.**
- 9 **Indredavik B, Bakke F, Slordahl SA, et al.** Treatment in a combined acute and rehabilitation stroke unit: which aspects are most important? *Stroke* 1999;**30** 917–23.
- ▶ **Analysis of the most important factors in determining why stroke unit care leads to improved outcome in the setting of a combined acute care and rehabilitation unit.**
- 10 **de Bruijn SF, Stam J.** Randomized, placebo-controlled trial of anticoagulant treatment with low-molecular-weight heparin for cerebral sinus thrombosis. *Stroke* 1999;**30**:484–8.
- ▶ **The largest trial of heparin for CVST, still including too few patients to draw conclusions.**
- 11 **Rothwell PM, Warlow CP.** Prediction of benefit from carotid endarterectomy in individual patients: a risk-modelling study. European carotid surgery trialists' collaborative group. *Lancet* 1999;**353**:2105–10.
- ▶ **An attempt to define subgroups of CEA patients with greatest benefit.**