CLINICAL MANAGEMENT

Diagnosis and management of transient ischaemic attacks in accident and emergency

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A transient ischaemic attack (TIA) is defined as the acute onset of focal neurological or monocular symptoms due to cerebrovascular disease that resolves completely in less than 24 hours. TIAs are common with an estimated incidence of 0.5 per 1000 population,¹ and therefore present frequently to accident and emergency (A&E) departments. It is important to make an accurate diagnosis as they have important prognostic implications. The risk of stroke following a TIA is approximately 11.6% (95% confidence interval (CI) 6.9 to 16.3) in the first year and approximately 5.9% per year (95% CI 4.3 to 7.5) in the first five years. This represents a 13-fold excess risk of stroke in the first year compared with people without TIAs. Patients who have had a TIA also have a greater risk of death compared with people without TIAs (risk ratio 1.4, 95% CI 1.1 to 1.8),² and are at increased risk of other serious vascular events, for example myocardial infarction.³ Cerebrovascular disease is however one of the most common causes of death that can be prevented by the modification of vascular risk factors and the institution of pharmacological and surgical interventions.⁴⁻⁶ For this reason the A&E physician should be able to make an accurate diagnosis, initiate screening tests to identify modifiable risk factors and treatable causes, and refer the patient appropriately to ensure that they are assessed for the need for further investigations and possible interventional treatment with minimal delay.

History

The diagnosis of a TIA is not always easy. Often the symptoms and signs have already resolved by the time the patient is seen and there are no confirmatory tests available. Even among experienced neurologists there is considerable interobserver variation in the diagnosis of a TIA.⁷ For this reason a detailed history is vital, not only from the patient but also from any eye witnesses.

The differential diagnosis of a TIA includes a large number of conditions (see box). With this in mind specific questions should be asked to try to reach the correct diagnosis; it is important to determine the exact nature of the onset of symptoms. With a TIA the key features are that the symptoms are: (1) focal; (2) occur suddenly; (3) are maximal at onset.

Differential diagnosis of a TIA

Migraine
Epilepsy
Intracranial tumour
Arteriovenous malformation
Giant aneurysm
Hypoglycaemia
Syncope
Subdural haematoma
Labyrinthitis
Meniere's disease
Benign vertigo
Myasthenia gravis
Malignant hypertension
Hyperventilation

In contrast the slow build up of a migrainous aura over 20-30 minutes would be unusual in a TIA. Similarly demyelination has a more gradual onset and may be suspected by the age of the patient and a history of previous episodes. It is important to ask the patient what they were doing at the time to establish what functions could have been affected, for example if the patient was involved in conversation it would be possible to say whether dysphasia was present or not.

Inquiry should be made specifically as to the presence of headache. While headache is said to occur in 16% of TIAs¹ its presence should alert one to the possibility of an alternative diagnosis. The possibility of subarachnoid haemorrhage, migraine, temporal arteritis, subdural haematoma, tumour, and malignant hypertension should all be considered if headache is present.

The UK TIA Study Group found that certain transient focal neurological symptoms were more likely to be associated with intracranial tumours in patients who were initially diagnosed as having had a TIA. These were pure sensory phenomena, focal jerking or shaking, loss of consciousness, and isolated aphasia or speech arrest.⁸ It is therefore important to consider the possibility of an intracranial tumour in patients with these symptoms. It is important to be cautious in diagnosing a TIA on the basis of symptoms such as loss of consciousness, dizziness, confusion, incontinence, and bilateral loss of vision as these may all be secondary to cerebral hypoperfusion due to primary cardiac disease.

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GENERAL HISTORY

A good detailed history is vital for identifying the possible cause of the TIA as this may affect both the immediate management and subsequent investigation and treatment. A history of hypertension, cardiac disease, diabetes mellitus, hypercholesterolaemia, and smoking should be sought as these are all important treatable vascular risk factors.⁹ The patient should be asked if there has been any recent history of injury especially to the head and neck. It is important to be aware that neck injury can cause carotid or vertebral artery dissection and this should not be missed.

It is also important to determine whether the patient has any coexisting medical problems which may be a contraindication to future anti-thrombotic or anticoagulation treatment or surgical intervention.

LOCALISATION

The history should try to establish which vascular territory is involved and what type of vascular pathology is likely as this has important implications for investigation and prognosis. Traditionally clinical classifications of strokes have divided them into those in the anterior (carotid) circulation and those in the posterior (vertebrobasilar) circulation. Carotid events are suggested by amaurosis fugax, dysphasia, and hemiplegia. Vertebrobasilar events are more variable in their presentation and include tetraparesis, crossed sensory/motor loss, diplopia, dysarthria, dysphagia, vertigo, cortical blindness, and ataxia.⁶ While this division may be useful in considering possible investigation and treatment, it is now thought to be more useful to distinguish cortical from subcortical TIAs since their investigation and prognosis differs.

DIFFERENTIATION BETWEEN CORTICAL AND SUBCORTICAL TIAs

TIAs can therefore be further subdivided into those involving cortical branch arteries and those involving the deep perforating arteries supplying subcortical areas.

Cortical TIAs, that is those involving areas supplied by cortical branch arteries, can involve either the posterior circulation or the anterior circulation. Those involving the posterior cerebral artery territory often present with visual field deficits. Other symptoms include ipsilateral cranial nerve palsy with contralateral

motor and/or sensory deficit, bilateral motor and/or sensory deficit, disorders of conjugate eye movement, cerebellar dysfunction without ipsilateral long tract deficit, and cortical blindness. Symptoms of cortical TIAs in the anterior circulation include dysphasia and unilateral motor or sensory disturbance. If the territory supplied by the anterior cerebral artery is involved then the leg is affected more than the arm. With middle cerebral artery territory the face and arm are affected more than the leg and there may be a hemianopia. Cortical branch arteries have anastomotic potential via the circle of Willis and thus produce variable areas of ischaemia. Cortical TIAs in the anterior circulation are most often associated with cardiogenic embolism or artery-artery embolism from an occluded or stenosed internal carotid artery. Such patients need to be investigated urgently with carotid Dopplers and angiography. Posterior cortical TIAs are the most aetiologically heterogeneous group and can be caused by almost any cause of cerebral ischaemia. Cortical strokes are usually more severe and have a much worse prognosis than subcortical strokes.

Subcortical TIAs are due to ischaemia in areas supplied by deep perforating arteries. These vessels have limited anastomotic potential and a restricted area of infarction is usual. Clinically those symptoms that suggest a subcortical TIA include pure motor symptoms, pure sensory symptoms, and ataxic hemiparesis. It cannot be reliably distinguished whether the deficit arises from the anterior or posterior circulation. Subcortical TIAs are usually due to small vessel disease. Evidence suggests there is a low frequency of significant carotid stenosis or cardiac source of embolism,¹⁰ therefore such patients tend not to need such urgent investigation with carotid Dopplers and do not usually benefit from carotid endarterectomy. If a stroke occurs due to occlusion of a single deep perforating artery the resulting restricted area of infarction is known as a "lacune". Such lacunar strokes are less extensive and have a better prognosis than cortical strokes. Lacunar TIAs and strokes make up approximately 25% of all cerebral ischaemic events. The text by Warlow *et al* gives a comprehensive description of the classification of TIA and stroke and correlates this with prognosis.¹⁰

Table 1 summarises the important symptoms to elicit in the history.

Table 1 Important symptoms to elicit in the history

Subcortical symptoms	Cortical symptoms	Symptoms suggesting alternative diagnosis
Pure sensory involvement	Anterior:	Gradual onset of symptoms
Pure motor involvement	Amaurosis fugax	Headache
	Dysphasia	Focal jerking or shaking
	Hemiparesis	Loss of consciousness
	Posterior:	Isolated aphasia
	Crossed motor/sensory loss	Speech arrest
	Tetraparesis	
	Either:	
	Visual field deficit	
	Dysarthria	
	Ataxia	
	Diplopia	
	Dysphagia	
	Vertigo	

Examination

A thorough clinical examination is important not only to detect the presence of any persisting neurological signs but also to look for any precipitating cause of the TIA.

A full neurological examination should be performed including fundoscopy to exclude the presence of papilloedema, retinal haemorrhages, cholesterol crystals, or changes indicative of malignant hypertension. Visual field examination should not be overlooked as deficits may be the only presenting feature of a TIA. Any neurological signs should be carefully documented in the A&E notes as they

Table 2 Key signs which should be sought in the examination

Neurological examination	Cardiovascular examination
Papilloedema	Atrial fibrillation
Retinal haemorrhages	Presence of peripheral pulses
Nystagmus	Hypertension
Visual field deficit	Carotid bruits
Cranial nerve deficit	Cardiac murmurs
Dysphasia	
Motor weakness	
Sensory disturbance	
Ataxia	

may have improved or resolved by the time the patient is seen by a member of the medical team.

In the cardiovascular examination it is important to look for the presence of an irregular pulse, hypertension, cardiac murmurs, and carotid bruits. The absence of a carotid bruit does not exclude carotid artery stenosis as one may not be heard with a very tight stenosis or occlusion. Atrial fibrillation, mitral stenosis, mitral valve prolapse, bicuspid aortic valve, aortic stenosis, and prosthetic heart valves may all be associated with a potential cardiac source of emboli.¹ It is important to check that the femoral pulses are palpable especially if the patient may be referred for angiography. Both radial pulses should be felt simultaneously as any inequality in timing suggests subclavian or innominate stenosis or occlusion.

Table 2 summarises key signs that should be sought in the examination.

After taking a thorough history and careful examination one should be able to assess the probability that the patient has suffered a vascular event and have a good idea where the lesion is likely to be and its relationship to the vascular supply. A vascular event is unlikely in a patient less than 40 years old with no symptomatic vascular disease and no vascular risk factors.⁹ The possibility of cocaine or amphetamine abuse should be considered in young patients with no other risk factors.

Investigation

Investigations in a patient with a TIA aim to identify the possible aetiology of the event, to establish a baseline of prognostic factors and hence prognosis, and to exclude other important diagnoses. Considerable variation exists in the way neurologists investigate patients suspected of having a TIA, although attempts have been made to identify the most cost effective strategy.¹¹ In the A&E department it is obviously not practicable to investigate extensively all patients suspected of having had a TIA. There are however certain baseline investigations that are appropriate where the results may directly influence the immediate management and subsequent investigation of the patient.

Blood tests that should be requested are a full blood count, erythrocyte sedimentation rate (ESR), and blood glucose. Patients who have polycythaemia, thrombocythaemia, or a raised ESR should be referred immediately for further investigation and treatment as they are at high risk of further episodes. Electrocardiography (ECG) should be performed, most

importantly to exclude atrial fibrillation as these patients may need immediate anticoagulation, but also to detect the presence of myocardial ischaemia, left ventricular hypertrophy, or arrhythmias. Serum cholesterol, venereal disease reference laboratory (VDRL) and *Treponema pallidum* haemagglutination (TPHA) tests, and urine analysis to exclude renal disease or diabetes are also considered to be first line investigations for all patients.¹¹ While some people may debate the need for these to be performed in A&E, it is probably justified in order that the results can be quickly available when they are seen in outpatients and the patient does not have to be bled twice. Studies on the yield of first line investigations, that is the proportion of tests performed which detect a pathogenically relevant or potentially treatable condition that influences management, show that the yield is greatest for plasma cholesterol (45%) and ECG (45%).¹¹

Other urgent investigations that may need to be done in A&E will be determined by the clinical picture. Blood cultures should be taken if the patient is febrile as infective endocarditis is a potential source of cardiac emboli. Thyroid function tests should be performed in those patients in atrial fibrillation. Plasma urea and electrolytes are indicated in patients who are hypertensive or taking diuretics or if there is doubt about the diagnosis of a TIA. Urgent chest radiography is indicated if the clinical or ECG findings show hypertension, left ventricular hypertrophy, or a possible cardiac source of embolism. In patients with clinical suspicion of cardiogenic embolism echocardiography should also be considered. Computed tomography of the head is indicated if the clinical picture raises the suspicion of an underlying structural intracranial lesion or a haemorrhage. The presence of low density lesions consistent with infarction does not mean that the classification changes from that of a TIA to a stroke.¹² As the yield from the routine screening of TIA patients with computed tomography is very low for detecting structural lesions (1%),¹¹ it is debatable whether all patients should have this investigation as a routine part of their subsequent outpatient work up.

If the symptoms have resolved and baseline investigations are normal then the patient can often be discharged home. Local policy will determine referral practices to ensure that the patient is investigated further as appropriate with the minimum of delay. Doppler or duplex carotid ultrasound examination is an excellent screening test to detect carotid stenosis and is indicated in patients with recent cortical TIAs. Studies have shown that it has high sensitivity in detecting 50% stenosis but that it is not able to accurately classify the more severe degrees of stenosis.¹³ As the risk of stroke diminishes with time,^{2,3} it is important that referral for ultrasonography is efficient in order that it is performed as soon as possible. Depending on the results of the ultrasound, angiography, magnetic resonance angiography, or spiral

Table 3 Investigation of TIAs

Minimum investigations in all patients with a TIA in A&E	Investigations in A&E if indicated by clinical findings	Outpatient investigations within two weeks	Further investigations if indicated by results of preliminary tests
Full blood count ESR Blood glucose Plasma cholesterol VDRL/TPHA ECG Chest radiography	Blood cultures Urea and electrolytes Thyroid function tests Computed tomography of the brain	Doppler/duplex carotid ultrasound (if cortical symptoms) Computed tomograph if not already one	Carotid angiography Magnetic resonance angiography Spiral computed tomography Echocardiography (if suspicion of cardiogenic embolism)

computed tomography may be required to further assess the extent of disease.¹⁴

In young people with TIAs other investigations that may be indicated include activated partial thromboplastin time, kaolin cephalin clotting time, and dilute Russell's viper venom time (to screen for lupus anticoagulant), protein C resistance, protein C, protein S, and antithrombin III.¹⁵ A temporal artery biopsy should be performed if temporal arteritis is suspected.

Table 3 summarises the most important investigations that should be carried out.

Treatment

Treatment strategies after a TIA aim to prevent further vascular events particularly a disabling stroke. They include modification of vascular risk factors, antiplatelet treatment, anticoagulation, and surgery. Obviously treatment options in the A&E department are limited; however, it is important that any possible preventative measures that can be instituted are done.

Hypertension is the most important treatable risk factor for stroke. It has been estimated that treating all hypertensives could reduce the mortality of stroke by 15%,¹ while treatment of an individual hypertensive patient could reduce their risk of stroke by up to 38%.⁹ A confidential inquiry into avoidable factors in deaths from stroke found that often hypertension is inadequately monitored and treated.⁴ While antihypertensive drugs should not routinely be started in A&E after a single high blood pressure reading, the finding of hypertension should be communicated to the general practitioner in order that it can be carefully monitored.

The patient should be given advice about possible lifestyle modifications, the most important being stopping smoking as this is the second most important preventable risk factor.⁹

Aspirin has been shown to significantly reduce the risk of stroke, myocardial infarction, and vascular death in patients with TIAs. A large meta-analysis from the Antiplatelet Trialists' Collaboration,¹⁶ showed that in people with previous minor stroke or TIAs aspirin gave an overall odds reduction of 22% (SD 4%) for vascular events and 23% (SD 6%) for non-fatal strokes (odds reduction is analogous to the relative risk reduction but slightly larger). Another meta-analysis of all trials in which aspirin was compared with placebo in patients with TIAs or minor strokes of presumably arterial origin showed that the overall reduction in relative risk associated with

low dose aspirin was 15% (95% CI -2 to 30) for stroke and 13% (95% CI -1 to 26) for stroke or vascular death.⁵

A large secondary prevention trial looking at patients with non-rheumatic atrial fibrillation and a history of TIA or minor ischaemic stroke in the previous three months showed that aspirin 300 mg daily reduced the annual incidence of vascular death, non-fatal stroke, non-fatal heart attack or systemic embolism from 19%/year to 15%/year compared with placebo (risk ratio 0.83, 95% CI 0.65 to 1.05) however this was not statistically significant.¹⁷

The optimal dose of aspirin has not been established by a properly designed, prospective, controlled study, although various studies have attempted to address the question.¹⁸ After a TIA it is generally recommended that 300 mg of aspirin is given immediately followed by low dose aspirin (75–150 mg daily). There are no definite data on how long treatment should be continued. Most neurologists would continue it indefinitely as long as no contraindications developed.

Ticlopidine is an alternative antiplatelet agent that may be more effective than aspirin in preventing stroke but which has more side effects.⁵ It is not generally used in the UK.

Recently a large multicentre trial has compared a new agent clopidogrel with aspirin.¹⁹ Clopidogrel is a thienopyridine derivative which inhibits platelet aggregation induced by adenosine diphosphate. The study demonstrated that long term administration of clopidogrel to patients with atherosclerotic vascular disease may be more effective than aspirin in reducing the combined risk of ischaemic stroke, myocardial infarction or vascular death (relative risk reduction of 8.7%, 95% CI 0.3 to 16.5). There was no statistically significant difference in the incidence of adverse effects.

It has been suggested that aspirin in combination with dipyridamole may be better than aspirin alone in the secondary prevention of stroke, although until recently trials have failed to prove a significant difference. The European Stroke Prevention Study 2 (ESPS2),²⁰ however, has reported that dipyridamole combined with aspirin was more effective than either alone. Future trials may help to resolve this problem.

In patients with non-rheumatic atrial fibrillation who have had a TIA anticoagulation with warfarin has been shown to reduce the risk of subsequent stroke by two thirds compared with placebo (risk ratio 0.34, 95% CI 0.20 to 0.57).¹⁷ Major bleeding problems were four times more common in those patients on war-

Figure 1 Algorithm for management of TIAs in the A&E department (CXR = chest radiography; ECG = electrocardiography; ESR = erythrocyte sedimentation rate; FBC = full blood count; GP = general practitioner; GLUC = glucose).

farin (2.8% per year) compared with those on aspirin (0.9% per year) and placebo (0.7% per year). At present there is no evidence that anticoagulants are better than aspirin in preventing strokes in patients who have had a TIA or ischaemic stroke who do not have atrial fibrillation, although some neurologists advocate giving warfarin to those patients without atrial fibrillation who are having recurrent TIAs not controlled with aspirin.⁹ Because of the increased risk of bleeding associated with warfarin caution should be exercised in patients with potential bleeding lesions and where there may be an increased risk of bleeding due to thrombocytopenia, liver failure, or renal failure. If the patient is at risk of falls, is likely to be uncooperative with long term treatment, or if there will be difficulties in monitoring the prothrombin time then the potential benefit must be judged to exceed the increased risk in these patients.

In the A&E department immediate anticoagulation with heparin may be indicated after consultation with a neurologist if the patient is having increasingly frequent TIAs with more than two in the previous 24 hours. In our hospital such patients who do not have any

contraindications are admitted for anticoagulation and urgent investigation.

Carotid endarterectomy significantly reduces the risk of stroke in patients with severe internal carotid artery stenosis (>70%) on the symptomatic side and who are otherwise fit enough to undergo surgery. Two large multi-centre trials have shown a highly statistically significant benefit in those treated with surgery. The European Carotid Surgery Trialists' Collaborative Group (ECST) showed a 36.3% relative risk reduction (95% CI 12.7 to 53.5) with a 7.5% incidence of perioperative death or disabling stroke.²¹ The North American Symptomatic Carotid Endarterectomy Trial Collaborators (NASCET) showed a 52.5% relative risk reduction (95% CI 27.6 to 69.3) with a 5.8% incidence of perioperative death or disabling stroke.²² The risk of stroke in patients with tight carotid artery stenosis who have had a TIA is approximately 10%. If the operative risk is judged to be less than this then they should be given the option of surgery.⁵ It is important that the A&E physician is aware of the risks and benefits of surgery in order that patients can be referred promptly if appropriate, remembering that it is only applicable to those patients with symptoms of cortical TIAs in the carotid territory, for example amaurosis fugax, dysphasia, and hemiparesis.

Figure 1 shows an algorithm for management of TIAs in the A&E department.

Summary

Stroke is an important cause of morbidity and mortality. Often the first presentation of cerebrovascular disease is a TIA which will present to the A&E department. Patients who have had a TIA are at increased risk of stroke, myocardial infarction, and vascular death. The risk of stroke after a TIA is greatest in the first year (approximately 11.6%) with a risk of approximately 5.9% per year over the first five years.² As the risk is highest in the first months following a TIA it is important that the patients are diagnosed accurately, investigated promptly, and referred appropriately for treatment in order that valuable time is not lost. For this reason A&E physicians have a valuable role in the initial assessment and management of the patient. It has been advocated that patients should be seen by a neurologist or physician with an interest in cerebrovascular disease within days of their symptoms and be prepared for surgery within two weeks after a TIA.¹ While it is usually not possible to achieve this ideal, improved cooperation between A&E physicians and these neurologists, general physicians, and geriatricians should lead to the implementation of speedy efficient referral procedures which can only improve patient care. When you next see a patient with a TIA in the A&E department remember what they have to lose.

Three questions relating to this article are:

- (1) How are TIAs subdivided and what clinical features allow this differentiation?
- (2) What are the initial investigations that should be performed in A&E?

- (3) When are the risks of completed stroke greatest after a TIA? Enumerate these risks. How effective is aspirin at reducing this risks?

The key references are Payne *et al*,⁴ Warlow *et al*,¹⁰ and the Antiplatelet Trialists' Collaboration.¹⁶

- 1 Humphrey PRD. Management of transient ischaemic attacks and stroke. *Postgrad Med J* 1995;71:577-84.
- 2 Dennis M, Bamford J, Sandercock P, *et al*. Prognosis of transient ischaemic attacks in the Oxfordshire community stroke project. *Stroke* 1990;21:848-53.
- 3 Hankey GJ, Slattery JM, Warlow CP. The prognosis of hospital referred transient ischaemic attacks. *J Neurol Neurosurg Psychiatry* 1991;54:793-802.
- 4 Payne JN, Milner PC, Saul C, *et al*. Local confidential inquiry into avoidable factors in deaths from stroke and hypertensive disease. *BMJ* 1993;307:1027-30.
- 5 Henry JM, Barnett MD, Eliasziw M, *et al*. Drugs and surgery in the prevention of ischaemic stroke. *N Engl J Med* 1995;332:238-48.
- 6 Hankey GJ. Transient ischaemic attacks. *Med J Aust* 1995;162:260-3.
- 7 Kraaijeveld CL, van Gijn J, Schouten HJA, *et al*. Interobserver agreement for the diagnosis of transient ischaemic attacks. *Stroke* 1984;15:723-5.
- 8 UK TIA Study Group. Intracranial tumours that mimic transient cerebral ischaemia: lessons from a large multi-centre trial. *J Neurol Neurosurg Psychiatry* 1993;56:563-6.
- 9 Hankey GJ, Warlow CP. *Transient ischaemic attacks of the brain and eye*. London: WB Saunders, 1994.
- 10 Warlow CP, Dennis MS, van Gijn J, *et al*. *Stroke. A practical guide to management*. Oxford: Blackwell Science, 1996.
- 11 Hankey GJ, Warlow CP. Cost effective investigation of patients with suspected TIAs. *J Neurol Neurosurg Psychiatry* 1992;55:171-6.
- 12 Dennis MS, Bamford JM, Sandercock PAG, *et al*. Computed tomography in patients with transient ischaemic attacks: when is a transient ischaemic attack not a transient ischaemic attack but a stroke? *J Neurol Neurosurg Psychiatry* 1990;237:257-61.
- 13 Sellar RJ. Imaging blood vessels of the head and neck. *J Neurol Neurosurg Psychiatry* 1995;59:225-37.
- 14 Lord RSA. Non-invasive testing for cerebrovascular disease. *Cardiovasc Surg* 1996;4:424-37.
- 15 Greaves M. Coagulation abnormalities and cerebral infarction. *J Neurol Neurosurg Psychiatry* 1993;56:433-9.
- 16 Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy. 1. Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994;308:81-106.
- 17 European Atrial Fibrillation Trial Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attacks or minor stroke. *Lancet* 1993;342:1255-62.
- 18 Dyken ML. Aspirin with and without dipyridamole. *Cerebrovasc Dis* 1997(suppl 6):10-16.
- 19 CAPRIE Steering Committee. A randomised, blinded trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;348:1329-39.
- 20 Diener HC, Cunha L, Forbes C, *et al*. European Stroke Prevention Study 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci* 1996;143:1-13.
- 21 European Carotid Surgery Trialists Collaborative Group. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis. *Lancet* 1991;337:1235-43.
- 22 North American Symptomatic Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high grade carotid stenosis. *N Engl J Med* 1991;325:445-53.