

The management of STROKE

By MOJGAN SANI, MBA, MRPHARMS, JODIE LACEY and ANTHONY RUDD, FRCP

The drug treatments available for stroke, and some of the trials which led to the acceptance of these treatments, are discussed in this article

Stroke kills approximately 90,000 women and 60,000 men annually in the UK. Although mortality rates have declined over the past 30 years, possibly due to improved awareness of treating risk factors such as hypertension and hyperlipidaemia, stroke still remains the third most common cause of death in the UK.¹ The estimated cost of stroke attacks to the NHS and social services is £2.3bn per year, nearly twice that of coronary heart disease (CHD).^{1,2}

Stroke causes long-term disability requiring specialised support and care for each individual patient, depending on the severity of the stroke and associated comorbidities. It results from either an occlusion of arteries (which reduces the blood supply to the brain) or rupture of an artery (which causes bleeding into part of the brain). Effective treatment needs to be targeted at the primary and secondary prevention of stroke, as well as the acute

phase of stroke, so as to minimise cerebral ischaemia.

DIAGNOSIS

The two types of stroke are haemorrhagic stroke and ischaemic stroke. Rapid diagnosis of stroke needs to be focused on the following:

- 1 Determining whether the symptoms are due to a stroke
- 1 Localising the brain injury
- 1 Establishing the type of stroke
- 1 Establishing the most likely cause of the stroke, taking into account the risk factors

Many patients experience nausea, vomiting, headache and impairment in consciousness, reflecting dysfunction in areas of the brain. Panel 1 (p38) shows the differential features of the two types of stroke. However, there is considerable overlap in the presenting symptoms and clinical diagnosis without imaging should not be relied upon in making a definitive diagnosis.

The most important diagnostic test to differentiate the two types of stroke is brain

imaging either by computed tomography (CT) or magnetic resonance imaging (MRI). These techniques have the ability to visualise bleeding and define the extent of cerebral damage. Until intracranial haemorrhage has been excluded, patients should not be treated with anticoagulants or thrombolytic agents.

HAEMORRHAGIC STROKE

Patients with intracranial bleeding caused by haemorrhagic stroke are more likely to have an increase in blood pressure and intracranial pressure than patients with ischaemic stroke. Apart from cerebellar haematomas, there is no evidence that surgical evacuation of haematomas is helpful. Management is therefore medical, with careful blood pressure control and maintenance of other physiological parameters such as temperature, hydration and oxygenation.

Anticoagulants and thrombolytic agents are the most common cause of a haemorrhage related to a disorder of coagulation. Symptomatic haemorrhagic transformation of the infarction or primary brain haemorrhage can complicate the use of low

Ms Sani is consultant pharmacist, Ms Lacey is senior pharmacy technician, cardiothoracic centre, and Dr Rudd is consultant physician, stroke unit, Guy's and St Thomas' Hospitals NHS Trust

Panel 1: Types of stroke

Haemorrhagic stroke

Prominent headache associated with nausea and vomiting
Early and prolonged loss of consciousness
Retinal haemorrhages
Neck rigidity
Focal signs (from a defined area) that do not fit the anatomic pattern of a single blood vessel

Ischaemic stroke

Focal neurologic symptoms and signs consistent with damage in an area of brain supplied by a single blood vessel
Associated atherosclerotic disease (cardiac murmurs, arrhythmias, arterial pressure abnormalities, asymmetry of peripheral pulses)

molecular weight heparin (LMWH) and other heparins in the treatment of acute ischaemic stroke.^{3,4} If the diagnosis is an intracranial haemorrhage, the following coagulation assessments should be made immediately:

- 1 Prothrombin time (PT) and international normalised ratio (INR)
- 1 Platelet count
- 1 Activated partial thromboplastin time (APTT)

Panel 2 shows treatment guidelines following the use of anticoagulants or thrombolytic drugs.

ISCHAEMIC STROKE

Measures to improve blood supply to the brain are the most commonly prescribed therapies for patients with ischaemic stroke.

Fibrinolytic agents Recombinant tissue-type plasminogen activator (rt-PA) converts plasminogen to plasmin, which in turn cleaves fibrin(ogen) and the fibrin matrix of the clot, and is useful in the treatment of acute ischaemic stroke. To be successful, it is vital that thrombolytic therapy is administered within the first few hours of ischaemic injury.⁵⁻⁷ The rationale behind the use of these agents in the acute phase of an ischaemic stroke is to accelerate reperfusion of the affected area of the brain.

Urokinase and single chain urokinase plasminogen activator (scu-PA) administered intravenously or intra-arterially are agents still undergoing tests to determine their success in the treatment of ischaemic stroke patients. There have been several trials using streptokinase which have shown increased rates of mortality, usually due to cerebral haemorrhage, and it is unlikely that there will be further trials with streptokinase.

In the National Institute of Neurological Disorders and Stroke Study (NINDS), rt-PA given within three hours of the onset of symptoms was associated with improved early and late outcome measurements. The dose of rt-PA was 0.9mg per kg (maximum 90mg) given over one hour. The results of this trial led to streptokinase becoming the first agent to be granted US approval for the treatment of ischaemic stroke.^{7,8} Current data support the intravenous use of rt-PA for carefully selected patients within three hours of the onset of symptoms. There is as yet no license for the use of rt-PA in the UK, and very few centres are using it. There is a further trial currently going on (International Stroke Trial [IST] 3) that is evaluating the use of rt-PA up to six hours after ischaemic injury.

To date, trials have shown an increase in disability and/or mortality largely due to symptomatic brain haemorrhage following intravenous administration.

Heparin anticoagulation therapy In the UK, neither unfractionated heparin nor LMWH are licensed for the treatment of ischaemic stroke and they should not be used for this indication. In the IST trial,³ patients with acute ischaemic stroke received subcutaneous unfractionated heparin, aspirin, both or neither. IST demonstrated that the use of subcutaneous heparin resulted in fewer recurrent ischaemic strokes within 14 days compared with no treatment. However, this was offset by a significant increase in the risk of haemorrhage. There was no significant difference in disability and death at six months.³

Oral anticoagulants Oral anticoagulants are usually the first choice for patients with cardioembolic stroke, a type of ischaemic stroke.

Warfarin or one of its derivatives is a suitable anticoagulant.⁹ These agents reduce plasma levels of active factors II, VII, IX and X, and proteins C and S. Because they are also antagonists of vitamin K, they interfere with the gamma-carboxylation of terminal glutamic acid residues of specific coagulation factors. Recent clinical trials confirm their efficacy and safety. Overall, they reduce the risk of thromboembolism (mainly stroke) by about 68 per cent in patients with atrial fibrillation.¹⁰

The dose prescribed is determined after taking into consideration the patient's PT using the INR. The level of coagulation has to be assessed frequently so that the patient is aware of the required dose.

Warfarin interacts with other medication and also certain foods; therefore the patient needs to be fully informed of the contraindications, as well as the safety measures required while taking it. Warfarin activity is increased by, in particular, alcohol, anabolic steroids, amiodarone, aspirin and other non-steroidal anti-inflammatory drugs, cimetidine, ciprofloxacin, clofibrate, co-trimoxazole, danazol, dipyridamole, erythromycin, glucagon, metronidazole, quinidine, simvastatin, tamoxifen, thyroxine and azole antifungals. The activity of warfarin is decreased by, in particular, barbiturates, carbamazepine, griseofulvin and phytomenadione.

The INR should be closely monitored whenever any drug is added to, or withdrawn from, the patient's therapeutic regimen. A change in the patient's clinical condition, particularly associated with liver disease, intercurrent illness, or drug administration, necessitates more frequent testing. Major changes in diet (especially involving salads and vegetables) can also affect warfarin control.

Panel 2: Guidelines for treating haemorrhage due to anticoagulants or thrombolytic agents

Warfarin or other anticoagulant

Stop warfarin or other oral anticoagulant
Administer 5mg–25mg intravenous (IV) Vitamin K or 2–3 units of plasma to replace factors II, VII, IX and X
Recheck the PT in six hours and if required, repeat plasma administration

Heparin

Stop heparin
Administer 30mg of protamine sulphate in a slow IV infusion and monitor activated partial thromboplastin time (APTT)

Streptokinase, urokinase or recombinant tissue-type plasminogen activator

Stop thrombolytic agent
Check haemoglobin, hematocrit, prothrombin time, APTT, platelet count and fibrinogen
Type and cross-match 4 units of blood
Give 4–6 units of cryoprecipitate to raise the fibrinogen level to >150mg/dl
Recheck the fibrinogen level every four hours and transfuse with cryoprecipitate to maintain fibrinogen level at >150mg/dl

The side effects of warfarin include haemorrhage. This is usually related to over-dosage and is more likely to occur in patients who are elderly or have liver disease. In rare cases, alopecia has been reported as a side effect of warfarin. Diarrhoea and rashes occasionally occur soon after starting therapy, in which case phenindione can be used instead.

Because it takes two to three days for oral anticoagulants to take full effect, heparin should be given to ensure immediate anticoagulation when warfarin is first started. The desired PT/INR for most situations is a level of 2–3.5 depending on the initial diagnosis. The risk of serious haemorrhage rises at an INR greater than 4. The national clinical guidelines for stroke advise that anticoagulation should not be started for two weeks after the acute event when it is being used for suspected cardioembolic stroke.¹¹

Antiplatelet agents Antiplatelet agents are the usual primary treatment for most patients with ischaemia secondary to arterial diseases. Antiplatelet agents include aspirin, dipyridamole, ticlopidine and clopidogrel.

Aspirin Aspirin inhibits platelet aggregation and the rationale for using it in the treatment of acute ischaemic stroke is to prevent further occlusion of blood supply to surrounding areas of brain tissue.

Two large trials, the IST³ and the Chinese Acute Stroke Trial (CAST),¹² have investigated the use of aspirin in over 40,000 patients. In the IST trial, patients were treated with aspirin 300mg daily for 14 days. When compared with patients taking placebo, these patients had significantly fewer recurrent ischaemic strokes (2.8 per cent in aspirin-treated patients compared with 3.9 per cent in placebo-treated patients) without any significant increase in haemorrhagic strokes (0.9 per cent in aspirin-treated patients compared with 0.8 per cent in placebo-treated patients). However, no significant effect was observed on mortality or six months outcome. In the CAST trial, patients were treated with aspirin, 160mg per day, for up to four weeks. After four weeks, there was a significant reduction in overall mortality (3.9 per cent reduced to 3.3 per cent). These trial results suggested that there was a small but definite benefit with aspirin.^{3,12}

Aspirin is the most commonly prescribed drug for primary or secondary prevention of ischaemic stroke in patients with arterial diseases.^{9,13} Aspirin interferes with platelet function and thromboxane-A₂ production by irreversible acetylation and inactivation of cyclo-oxygenase. It is also used as an alternative to oral anticoagulants for those who cannot tolerate warfarin. Aspirin therapy should be started within 48 hours of stroke. Where brain imaging is not available during

this period and the clinical suspicion of haemorrhage is low, aspirin can be considered. Subgroup analysis of the IST and CAST data, looking at patients who received aspirin inadvertently, despite subsequently being shown to have a haemorrhage, showed that their outcomes were not significantly impaired.

Although aspirin is inexpensive and easy to administer, it is not without side effects. The most common side effects are gastritis, peptic ulcer bleeding and upper gastrointestinal (GI) bleeding. When aspirin is administered at low doses (less than 100mg daily), the patient is less likely to experience any major GI side effect. There are enteric-coated preparations available to protect the stomach from irritation. Earlier studies have demonstrated efficacy of daily doses higher than 1,000mg, while more recently, much lower doses (50mg to 325mg daily) have shown some usefulness in the prevention of stroke.^{13,14}

Dipyridamole When used alone, dipyridamole has shown antiplatelet effects similar to those of low-dose aspirin. Dipyridamole can also be used as an adjunct to warfarin. The most common side effect is headache.

Aspirin plus dipyridamole Combination therapy with aspirin and dipyridamole may be beneficial because it affects platelets through different mechanisms and may therefore be preferable to prescribing each drug alone.

The European trial, European Stroke Prevention Study (ESPS) 2, using doses of 50mg aspirin and 400mg extended-release dipyridamole daily, showed the effectiveness of using a combination therapy.¹⁷ It is an option for management when a patient has ischaemic symptoms despite treatment with aspirin

alone. The study suggests that there is some synergism between aspirin and dipyridamole.

Ticlopidine Ticlopidine is a potent antiplatelet agent that blocks adenosine-5-diphosphate-induced platelet aggregation. In one trial comparing the two drugs, ticlopidine was approximately 15 per cent more effective than aspirin.¹⁵ In the US, ticlopidine is indicated for stroke prevention where the patient cannot tolerate aspirin.

The usual dose of ticlopidine is 250mg to 500mg daily. Unfortunately, it has a poor side effect profile (diarrhoea, allergic skin reactions, neutropenia and thrombocytopenia). Bi-weekly monitoring of white blood cell and platelet counts is required during the first three to four months of treatment due to the haematological complications.

Clopidogrel Clopidogrel is in the same class of drugs as ticlopidine. However, the risk of haematological complications is lower with clopidogrel than with ticlopidine. The CAPRIE trial investigated the use of clopidogrel against aspirin in patients with ischaemic heart disease, cerebrovascular disease and peripheral vascular disease.¹⁶ In the study, 19,185 patients were given either 75mg clopidogrel or 325mg aspirin. The study results showed a small but significant benefit in reducing stroke, myocardial infarction or vascular death in the clopidogrel group (relative risk reduction of 8.7 per cent in favour of clopidogrel, $P=0.043$).

— STROKE PREVENTION

The presumed cause of stroke determines the prophylaxis. Figure 1 (p40) is a flow-chart for the prevention of stroke or recurrent stroke based on presumed cause and arterial territory (the area of brain supplied by a particular vessel).

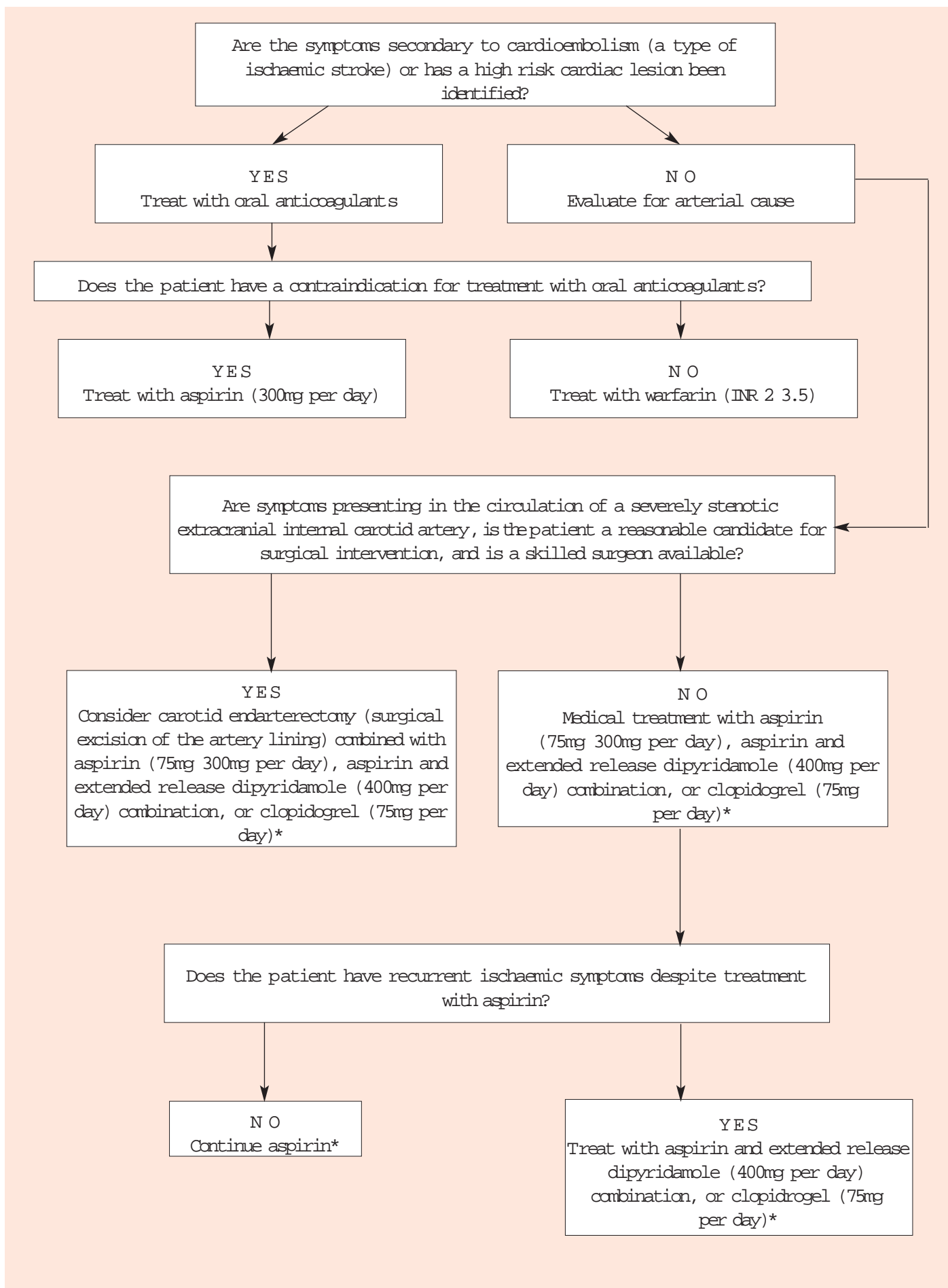


Figure 1: Algorithm for prevention of stroke or recurrent stroke based on presumed cause and arterial territory (area of brain supplied by a particular vessel)
 *Patients who are allergic or intolerant to aspirin can be treated with clopidogrel (75mg per day) or extended release dipyridamole

The role of statins The available data suggest that any patient with a history of ischaemic stroke or transient ischaemic attack (TIA) and CHD, and a cholesterol concentration greater than 5mmol per litre (or low density lipoprotein cholesterol higher than 3mmol per litre) is likely to benefit from cholesterol reduction with a statin. By contrast, it seems premature to recommend routine use of statins in patients with ischaemic stroke or TIA and no history of CHD until ongoing trials are completed.

ACE inhibitors in stroke prevention Large reductions in the risk of recurrent strokes and cardiovascular events were achieved in the PROGRESS (perindopril protection against recurrent stroke study) trial.¹⁸ This was a six-year double-blind placebo-controlled trial that recruited over 6,000 stroke sufferers worldwide. Patients were randomised to receive the angiotensin converting enzyme (ACE) inhibitor perindopril 4mg (and the diuretic indapamide in those with no definite indication or contraindication to treatment with a diuretic) versus placebo. Both hypertensive and non-hypertensive patients were included in the study.

The primary objective of the study was to determine the effects of a long-term ACE inhibitor based blood pressure lowering regimen on the risk of stroke or TIA. Secondary objectives included the effects of treatment on total cardiovascular events, dementia and disability.

The results of the trial at five years showed a reduction of 28 per cent in strokes ($P < 0.0001$). The number of haemorrhagic strokes were halved and ischaemic strokes were reduced by 24 per cent. Fatal strokes were reduced by 38 per cent and the combined end-point of stroke, heart attack and death from any cause was reduced by 26 per cent. The study also found a risk reduction of 34 per cent for dementia and 45 per cent for severe dementia. The benefits of combination treatment were irrespective of age and blood pressure at entry. Even patients with a systolic blood pressure below 140 saw a 40 per cent risk reduction in recurrent stroke.

REHABILITATION

Rehabilitation should begin immediately after stroke and involve all relevant health care professionals, including physiotherapists, speech and language therapists, psychologists, nurses, pharmacists, dietitians, occupational therapists and social workers. The rehabilitation programme should be individually designed according to the physical and neurological consequences resulting from the stroke.

Complications after stroke are common. Depression affects up to 50 per cent of patients and can hinder recovery from stroke. Therefore, the use of antidepressants

such as tricyclic drugs or serotonin agonists, in addition to specialist counselling, may be an important part of rehabilitation. There are as yet, however, no trials with sufficient power to show any benefit of antidepressant medication following stroke.

The main goal in discharge planning is to provide continued long-term medical treatment and rehabilitation that meets the wishes and needs of patients and their families.

CONCLUSION

It is clear to see that following medical trials and studies, current efforts on controlling and managing existing cerebrovascular high risk factors such as hypertension, could have a dramatic effect on mortality and morbidity rates in such patients.

Stroke patients frequently require prolonged hospital stays, followed by community or nursing home care, which is a major drain on health care funding, accounting for 6 per cent of total NHS and social services expenditure. With more people surviving stroke and a rapidly increasing aged population, this figure can only increase if more effective strategies for prevention, treatment and rehabilitation are not established.

There is a need to focus on highlighting the risk factors for stroke and increase awareness in those patients at risk, ensuring strict compliance with medical therapies so that such factors are controlled, thus reducing the risk of suffering a stroke.

It is also vital that following a stroke, patients comply fully with their drug regimen and thus avoid a recurrent attack. This can be extremely difficult without full specialist support services, especially when a patient is mentally and physically impaired.

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