Secondary prevention of stroke

Introduction

The risk of recurrent stroke is greatest early: about 2–3% of stroke survivors have a recurrent stroke within the first 30 days, about 9% in the first 6 months and 10–16% within 1 year, which is about 15 times greater than the risk in the general population. After the first year, the average annual risk of recurrent stroke for the next 4 years falls to about 5%, this being about 9 times the risk of stroke in the general population (Burn et al, 1994; Mohan et al, 2011). This article describes issues surrounding stroke prevention and outlines specific treatment options.

Lifestyle modification

Lifestyle modification consisting of weight loss in overweight patients, increased physical activity and a diet consisting of more than five portions of fruit and vegetables per day, two portions of fish per week and reduced saturated fat is suggested in all patients (He et al, 2006; Fung et al, 2008; Hooper et al, 2012; Royal College of Physicians, 2012). In addition, reduced sodium and alcohol intake reduces systolic blood pressure and is also recommended (Royal College of Physicians, 2012; He et al, 2013). Indeed, patients should be advised to ensure that their alcohol intake is less than 2 units per day as an intake greater than this predisposes to hypertension.

Cigarette smoking increases stroke risk by at least 1.5-fold. Consequently, patients should be provided with advice to stop smoking cigarettes, and aids such as nicotine replacement therapy may be used. Both ischaemic and haemorrhagic stroke may be caused by recreational substance misuse and individuals should be advised not to use recreational drugs in view of the potential adverse effects.

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Treatment of hypertension

High blood pressure is the most important treatable and causal risk factor for stroke. A meta-analysis of individual data for 1 million adults demonstrated that throughout middle and old age, usual blood pressure is strongly and directly related to stroke-related mortality, without any evidence of a threshold down to at least 115/75 mmHg. More specifically, at ages 40–69 years, each difference of 20 mmHg usual systolic blood pressure (or, approximately equivalently, 10 mmHg usual diastolic blood pressure) was associated with more than a twofold difference in the stroke death rate. These proportional differences were about half as extreme at ages 80–89 years as at ages 40–49 years, but the annual absolute differences in risk were greater in old age. The age-specific associations were similar for men and women, and for cerebral haemorrhage and cerebral ischaemia (Lewington et al, 2002).

A meta-analysis of 147 randomized controlled trials involving 464 000 participants has shown that antihypertensive treatment in individuals with hypertension reduces stroke incidence by 41% for a blood pressure reduction of 10 mmHg systolic or 5 mmHg diastolic (Law et al, 2009). Furthermore, trial data have shown that modest lowering of blood pressure in both hypertensive and non-hypertensive individuals reduces the risk of recurrent stroke, with lowering of blood pressure by 9/4 mmHg producing a 28% relative risk reduction in subsequent stroke over 4 years of follow up and lowering of blood pressure by 12/5 mmHg producing a 43% relative risk reduction in subsequent stroke over a similar time period (PROGRESS Collaborative Group, 2001).

Current guidelines advocate that treatment should be initiated and/or increased as is necessary or tolerated to consistently achieve a clinic blood pressure below 130/80 mmHg, except for patients with severe bilateral carotid stenosis, for whom a systolic blood pressure target of 130–150 mmHg is appropriate.

For patients aged 55 years or over, and African or Caribbean patients of any age, antihypertensive treatment should typically be initiated with a long-acting dihydropyridine calcium-channel blocker and/or a thiazide-like diuretic. If target blood pressure is not achieved, an angiotensin-converting enzyme inhibitor or angiotensin-II receptor blocker should be added.

For patients not of African or Caribbean origin or younger than 55 years, the first choice for initial antihypertensive therapy should be an angiotensin-converting enzyme inhibitor or angiotensin-II receptor blocker (Royal College of Physicians, 2012).

There has been considerable controversy about how soon after stroke blood pressure should be lowered and it is the subject of ongoing research (Robinson and Potter, 2004; Ntaios et al, 2010). This is because cerebral autoregulation may be impaired in acute stroke patients (Dawson et al, 2000) and adequate perfusion of the brain, especially in the infarcted region, may depend upon blood pressure. It is estimated that 7–10 days may be required to restore cerebral autoregulation and national guidelines advise that new antihypertensive treatment should be delayed until 1 week post stroke (Royal College of Physicians, 2012).

There are circumstances, however, when treatment may be offered earlier and data support early antihypertensive therapy when the mean of at least two blood pressure measurements is ≥200 mmHg systolic and/or ≥110 mmHg diastolic 6–24 hours after stroke or ≥180 mmHg systolic and/or ≥105 mmHg diastolic 24–36 hours after stroke (Schrader et al, 2003).

Management of diabetes mellitus

Diabetes mellitus is an independent risk factor for stroke and the mortality and disability of diabetics affected by stroke is significantly worse than that of non-diabetics (Mankovsky and Ziegler, 2004; Bhalla et al, 2013). If blood glucose levels are elevated after stroke, fasting blood glucose levels and/or glucose tolerance tests should be undertaken to facilitate the diagnosis and optimal management of patients with impaired glucose tolerance and diabetes mellitus. A target glycated haemoglobin in the secondary prevention of stroke is <7.5%.

Management of dyslipidaemia

Epidemiological and observational studies have not shown a clear association between cholesterol concentrations and all causes of stroke (Thrift, 2004). However, randomized controlled trials of cholesterol-lowering therapy with statins in 70 020 patients with established or high risk for coronary heart disease showed that statins decrease stroke incidence with relative and absolute risk reductions of 21% and 0·9% respectively (Amarenco et al, 2004).

The SPARCL (Stroke Prevention with Aggressive Reduction of Cholesterol Levels) trial is the only published study investigating the efficacy of statin therapy in the secondary prevention of stroke or transient ischaemic attack in patients without a past history of coronary events and this demonstrated atorvastatin 80 mg once daily to provide a hazard ratio for ischaemic stroke of 0.79 (95% confidence interval = 0.66–0.95) compared with placebo and a hazard ratio for haemorrhagic stroke of 1.68 (95% confidence interval = 1.09–2.59) compared with placebo (Amarenco et al, 2006).

The Cholesterol Treatment Trialists' Collaboration's meta-analyses of randomized controlled trials confirmed more intensive (e.g. 40–80 mg atorvastatin or 10–20 mg rosuvastatin) statin therapy regimens to provide a 16% relative risk reduction in stroke when compared to less intensive (e.g. 20–40 mg simvastatin) statin therapy regimens (Cholesterol Treatment Trialists' Collaboration, 2010). It has been estimated that about two-thirds of the gain from statin therapy is realized by the initial dose. While the relative risk reductions remain consistent as low-density lipoprotein cholesterol is lowered further, the absolute benefits become smaller. These results have led to current guidelines advocating use of simvastatin 40 mg daily in ischaemic stroke, intensified to 80 mg daily if total cholesterol remains >4.0 mmol/litre or low-density lipoprotein cholesterol remains >2.0 mmol/litre, and avoidance of statins in haemorrhagic stroke (Royal College of Physicians, 2012).

Antiplatelet agents

While current data do not support antiplatelet treatment for the primary prevention of stroke, a large body of evidence exists for three different antiplatelet agents with varying mechanisms of action (aspirin, dipyridamole and clopidogrel) in secondary prevention of stroke (Antithrombotic Trialists' Collaboration, 2002). Large randomized controlled trials involving tens of thousands of patients worldwide have demonstrated the beneficial effect of aspirin treatment in the secondary prevention of ischaemic stroke (Chen et al, 2000). Giving aspirin to patients who have had an ischaemic stroke in doses above 75 mg daily reduces the risk of stroke by about 13% and the stroke risk per year from 7% to 6%. This equates to 1 stroke being prevented for every 100 patients who are prescribed aspirin (Department of Health, 1997).

While aspirin is more effective than dipyridamole for stroke prevention, a meta-analysis of individual patient data from randomized controlled trials has shown that the combination of aspirin with dipyridamole reduces the risk of subsequent transient ischaemic attack and stroke by 18% compared with aspirin alone (Antithrombotic Trialists' Collaboration, 2002; Verro et al, 2008).

In patients with previous ischaemic stroke, myocardial infarction or symptomatic atherosclerotic peripheral arterial disease, the CAPRIE trial showed clopidogrel to reduce significantly the annual risk of ischaemic stroke, myocardial infarction or vascular death to 5.32% compared with 5.83% with aspirin ($P = 0.04$) (CAPRIE Steering Committee, 1996). Although this study was not designed specifically to address secondary prevention of stroke, post-hoc analyses showed that the benefit of clopidogrel was amplified in diabetic patients and those receiving lipid-lowering therapy.

More recently, the PROFESS trial showed there to be similar rates of recurrent stroke in patients randomized to the combination of aspirin plus extended-release dipyridamole *vs* clopidogrel (Sacco et al, 2008).

Two randomized controlled trials have also studied the effectiveness of clopidrogel in combination with aspirin for secondary prevention of stroke. While the CARESS study in patients with significant carotid artery disease demonstrated a reduction in the number of embolizations from unstable atheromatous plaques, the MATCH study showed that adding aspirin to clopidogrel in high-risk patients with recent ischaemic stroke or transient ischaemic attack was associated with a non-significant difference in reducing major vascular events but an increased risk of major bleeding (Diener et al, 2004; Markus et al, 2005). There is no evidence as yet to support triple antiplatelet therapy (with aspirin, dipyridamole and clopidogrel) and studies are ongoing to investigate this further and also to investigate newer antiplatelet agents such as prasugrel and ticagrelor.

Given the high early risk of recurrent stroke, strategies of early antiplatelet therapy have been investigated. The Chinese Acute Stroke Trial demonstrated a 24% relative risk reduction of recurrent stroke when aspirin was provided within 48 hours of ictus and the CHANCE trial, testing a combination of aspirin and clopidogrel *vs* aspirin for 21 days, followed by monotherapy for up to 3 months, demonstrated a 32% reduction in recurrent stroke in those randomized to dual antiplatelet therapy (CAST Collaborative Group, 1997; Gorelick and Farooq, 2014).

In view of the aforementioned body of evidence, the most recent national guidelines recommend:

- Clopidogrel as the first-line antiplatelet agent to be used in the secondary prevention of ischaemic stroke and the combination of aspirin with dipyridamole to be used for people who are intolerant of clopidogrel or in whom clopidogrel is contraindicated
- If both clopidogrel and modified-release dipyridamole are contraindicated or not tolerated, offer aspirin 75 mg daily and if both clopidogrel and aspirin are contraindicated or not tolerated offer dipyridamole (Royal College of Physicians, 2012).

Anticoagulation

Approximately one in five ischaemic strokes is cardioembolic (Palacio and Hart, 2002) and evidence exists for both primary and secondary prevention of cardioembolic stroke associated with atrial fibrillation most commonly, valvular heart disease and other cardiac disorders with embolic potential. While antiplatelet therapy reduces recurrent cardioembolic risk, randomized controlled trials have

shown anticoagulation to be superior (odds ratio of stroke 0.49, 95% confidence interval = 0.33–0.72) (Saxena and Koudstaal, 2004). A number of different anticoagulant treatments exist including heparins, warfarin and direct oral anticoagulants such as the thrombin inhibitor dabigatran and factor Xa inhibitors rivaroxaban and apixaban.

Warfarin provides an absolute annual recurrent stroke risk reduction of approximately 8% with a number needed to treat of 13 (Hankey, 2014). However, this is dependent on compliance with medication administration, monitoring and time in therapeutic range. Although they lack an antidote and are more costly, direct oral anticoagulants do not require monitoring and have a fixed dose-dependent effect that has been examined in large randomized controlled trials. The RE-LY and ROCKET-AF trials showed dabigatran and rivaroxaban respectively to be non-inferior to warfarin for preventing stroke and systemic embolism from atrial fibrillation and the ARISTOTLE trial showed apixaban to be superior to warfarin in preventing stroke or systemic embolism (1.27% per year in the apixaban group *vs* 1.60% per year in the warfarin group (hazard ratio = 0.79, 95% confidence interval = 0.66–0.95, $P=0.01$), with less bleeding and lower mortality (Connolly et al, 2009; Granger et al, 2011; Patel et al, 2011).

Current guidelines recommend:

- Dose-adjusted warfarin, unless there is a specific contraindication, with a target international normalized ratio of 2 to 3, except in patients with prosthetic heart valves who need a higher intensity of anticoagulation
- For patients where treatment with warfarin has proved impractical or poorly controlled, or resulted in allergy or intolerance, a direct oral anticoagulant should be used
- For patients with contraindications to anticoagulation, measures should be taken to reduce bleeding risk, using a tool such as 'HAS-BLED' to identify modifiable risk factors (Pisters et al, 2010). If after intervention for relevant risk factors the bleeding risk is considered too high for anticoagulation, antiplatelet treatment should not be used as an alternative. In selected cases, a left atrial appendage occlusion device may be appropriate (Royal College of Physicians, 2012).

There is a degree of uncertainty, however, over how long after a cardioembolic ischaemic stroke secondary prevention with anticoagulants should be started. Current guidelines advocate that anticoagulation should not be started until 14 days have passed from the onset of an ischaemic stroke in order to reduce the risk of intra-cranial haemorrhage (Royal College of Physicians, 2012). In some circumstances, however, such as in the setting of minor stroke with small infarct size on brain imaging and a high risk of cardioembolism, anticoagulation may provide benefit acutely under specialist supervision.

Management of cervical arterial disease

The North American Symptomatic Carotid Endarterectomy Trial (NASCET) Collaborators and European Carotid Surgery Trial (ECST) established that carotid endarterectomy reduces the risk of recurrent stroke in patients with symptomatic internal carotid artery stenosis (European Carotid Surgery Trialists' Collaborative Group, 1991; North American Symptomatic Carotid Endarterectomy Trial Collaborators, 1991).

Meta-analyses of randomized controlled trials demonstrated that carotid endarterectomy provided an absolute risk reduction of 4.6% in patients with 50–69% stenosis ($P=0.04$) and of 16% in patients with 70–99% stenosis without near-occlusion ($P<0.001$) (Rerkasem and Rothwell, 2011). Evidence of benefit is lacking in patients with near-occlusions or less than 50% stenosis. Benefit from surgery was greatest in men and in patients randomized within 2 weeks of their last ischaemic event, and fell rapidly with increasing delay. Indeed, current national guidelines recommend carotid endarterectomy within 1 week (Rothwell et al, 2004; Royal College of Physicians, 2012).

Age per se is not a contraindication to surgery and particular benefit has been demonstrated in patients over 75 years. However, many older patients have comorbidities that may increase surgical risk and careful preoperative assessment is essential. Carotid angioplasty or stenting have been developed as alternatives to surgery and may be carried out in patients where carotid endarterectomy is technically difficult or for medical reasons but peri-procedural stroke risk is increased with stenting.

In contrast to the strong evidence base for carotid endarterectomy for symptomatic carotid stenosis, surgical intervention is not currently advocated for asymptomatic carotid stenosis or external carotid or vertebral arterial disease. In patients with stroke secondary to cervical arterial dissection, meta-analysis of 1636 patients in 40 non-randomized studies showed no significant difference between antiplatelet (3/499, 2.6%) and anticoagulant (20/1137, 1.8%) therapy in preventing recurrent stroke (Kennedy et al, 2012) and treatment should therefore be either with antiplatelets or anticoagulants, preferably as part of a clinical trial, in view of the current uncertainty surrounding optimal therapy.

KEY POINTS

- Patients who have suffered a stroke or transient ischaemic attack have an increased risk of further stroke and must be urgently referred to specialist services for acute care and secondary prevention.
- Evidence-based guidelines exist for stroke prevention.
- Key areas include lifestyle modification, management of high blood pressure, diabetes mellitus and lipids, antithrombotic drug therapy and carotid surgery for symptomatic carotid stenosis.
- Specialist multidisciplinary stroke services play a major role in directing stroke prevention strategies.

Conclusions

Considerable evidence in the literature supports an active approach towards prevention of stroke. Much of this evidence comes from randomized controlled trials and systematic reviews that have considered risk factors and identified treatments which are both clinically and cost effective. There is evidence to suggest that early initiation of secondary prevention interventions is favourable and specialist stroke services have a pivotal role to play in ensuring that patients understand the rationale for their treatment, are motivated, comply with advice and are monitored for maximum benefit. **BJHM**

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