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Review

Drug treatments in the secondary prevention of ischaemic stroke

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ABSTRACT

Stroke is an important cause of death and disability. However, about two thirds of cerebrovascular events are initially minor. They carry a high risk of potentially severe recurrent events, but they also offer an opportunity for secondary prevention to avoid such recurrences. As most recurrent events occur within a short time after the initial presentation, secondary prevention has to be started as soon as possible. Dramatic risk reduction can be achieved with well-established drugs if used in a timely manner. A standard secondary preventive regimen will address multiple vascular risk factors and will usually consist of an antiplatelet agent, a lipid lowering drug, and an antihypertensive agent. Depending on the risk factor profile of each patient, this will have to be adjusted individually, for example, taking into account the presence of cardioembolism or of stenotic disease of the brain-supplying arteries. In recent years, the approach to treating these risk factors has evolved. In addition to absolute blood pressure, blood pressure variability has emerged as an important contributing factor to stroke risk, which is affected differently by different antihypertensive agents. New oral anticoagulants reduce the risk of cerebral haemorrhage and the need for regular blood checks. The best antiplatelet regimen for stroke prevention is still uncertain, and treatment of dyslipidaemia may change if trials with cholesteryl ester transfer protein (CETP) inhibitors, which increase levels of HDL-cholesterol, are successful. This article reviews the current evidence for drug treatments in the secondary prevention of ischaemic stroke.

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1. Background

Every year 150,000 people in the United Kingdom and 795,000 people in the US have a stroke, roughly equalling 1 stroke every 5 min in the UK and 1 stroke per minute in the US [1,2]. Stroke is a leading cause of death and disability in the world, and with the population ageing, its incidence is set to rise. Interest in the prevention and treatment of stroke has therefore grown considerably over the last years. Much of this interest has focussed on the treatment of acute disabling stroke, and the best ways to promote the use of thrombolytic therapy to limit infarct size and improve outcome. It is perhaps less widely recognised that about two thirds of patients initially have a minor, non-disabling cerebral ischaemic event. Such patients are at a high risk of having a further,

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potentially disabling stroke, but if treated appropriately, this risk can be reduced considerably. This review will focus on the currently available drug treatments in secondary stroke prevention.

2. The need for urgent investigation and treatment

After a transient ischaemic attack (TIA) or minor stroke, the risk of having a further event is highest in the acute phase: 8–12% of patients will have a stroke within a week, and 11–15% within the first month following their initial event [3]. To be effective, any intervention therefore has to be started as soon as possible. Several studies have shown that by starting secondary preventive treatments urgently, the 30-day-risk of recurrent stroke can be reduced by up to 80% [4–6].

3. Antiplatelet drugs

Antiplatelet agents are one of the mainstays of secondary preventive treatment in patients with non-cardioembolic ischaemic stroke. Of the available drugs, aspirin has been around the longest and has been studied extensively. In patients with stroke or TIA, using aspirin over 2 years compared to placebo will lead to five fewer deaths, 25 fewer non-fatal strokes and six fewer myocardial infarctions per 1000 people treated. While there will also be an additional seven extracranial non-fatal haemorrhages, on balance these numbers clearly favour the use of aspirin [7,8]. As an added benefit, long-term use of aspirin has also been reported to reduce death from cancer by 20 per 1000 people treated over 10 years [9]. While the use of aspirin is well established, some uncertainties remain. There have been no head-to-head comparisons of different doses, and efficacy appears to be similar from 50 mg to 900 mg/day. There are only few data available for doses <50 mg, and the risk of haemorrhage, increases above 100 mg/day, so that generally daily doses of 50–100 mg/day are recommended [7,8].

Dipyridamole is a phosphodiesterase inhibitor that is used in combination with aspirin in stroke prevention. Initial studies showed a higher efficacy of combination therapy in preventing non-fatal ischaemic stroke, with little effect on mortality or risk of haemorrhage compared to aspirin alone. However, there were some concerns about data quality, and later studies suggested that the reduction of stroke risk might be lower than the early studies had shown [8,10]. Compared to aspirin alone, combination therapy with aspirin and dipyridamole reduces the risk of recurrent stroke by 1% per year. However, it is also less well tolerated, with headache the main side effect, and twice daily dosing perhaps less convenient for patients.

Over recent years clopidogrel, a platelet ADP receptor antagonist, has been increasingly used in stroke prevention. The CAPRIE trial showed that compared to aspirin, clopidogrel reduced the annual rate of ischaemic stroke, myocardial infarction or vascular death from 5.83% to 5.32% (RRR = 8.7% [95% CI = 0.3–16.5, $p = 0.043$]), although this risk reduction did not reach statistical significance when only considering the subgroup of patients who had initially presented with a stroke [11]. Nevertheless, this trial and others showed that clopidogrel was at least as effective as aspirin, and the PRoFESS study, which compared the combination therapy of aspirin and dipyridamole to monotherapy with clopdiogrel, found that both drugs had very similar efficacy, i.e. compared to aspirin alone, the risk of recurrent stroke was reduced by 1% per year [10]. Potential advantages of clopidogrel include its better tolerability compared to dipyridamole, and once daily dosing. While some recent laboratory studies suggested that the efficacy of clopidogrel may be reduced with concurrent use of proton-pump inhibitors (PPIs), especially omeprazole and esomeprazole, it is uncertain if this translates into any reduction in clinical effectiveness. Nevertheless, the use of PPIs should be avoided in patients on clopidogrel, and other stomach protection should be used [2,12].

Combination therapy with aspirin and clopidogrel is widely used in coronary heart disease, but not established in stroke prevention. This is mainly due to any reduction in the occurrence of cerebral ischaemic events being offset by an increased risk of haemorrhage [1,2,13,14]. However, there may be a benefit in using combination therapy with these drugs for a limited time in the acute phase after a cerebral ischaemic event, as in this high risk period the reduction of ischaemic events may outweigh the increased risk of haemorrhage. This is supported by a recent meta-analysis, which suggested that dual antiplatelet therapy appeared to be safe and effective in preventing recurrent stroke and combined vascular events in patients with acute TIA and stroke, when compared to monotherapy [15]. However, this was a non-pre-specified subgroup analysis of several trials, which included combinations of different antiplatelet agents. The authors stated that their findings still needed testing in prospective studies. Currently, the only definite indication for combination therapy with aspirin and clopidogrel in secondary stroke prevention is in patients who have undergone endovascular treatments, such as carotid or vertebral artery stenting.

There are a number of other antiplatelet drugs available. These include ticlopidine, cilostazole and triflusal. Ticlopidine may be somewhat more effective than aspirin in preventing ischaemic events, but it also has potentially life threatening side-effects, such as severe neutropaenia and thrombocytopaenic purpura. Cilostazole and triflusal are used in some parts of the world, but it is not clear if they offer any benefit over aspirin, and their use is not internationally established [2].

4. Oral anticoagulation

The main indication for using anticoagulation in the prevention of ischaemic stroke is in patients with a cardioembolic source of stroke, most often non-valvular atrial fibrillation. This is the commonest type of cardiac arrhythmia, and its prevalence increases with age, with 15–20% of over 80-year-olds affected [16]. Several factors, such as age, the presence of diabetes, hypertension and congestive cardiac failure, as well as a history of a previous cerebrovascular events, influence stroke risk in patients with atrial fibrillation. Annual stroke risk differs between 1 and 20%, dependent on age and other risk factors. Anticoagulation leads to a relative risk reduction of 68%, making this the treatment of choice in such patients. Warfarin is still the most commonly used drug, with a target INR of 2.0–3.0 most widely accepted [2,16]. However, the use of Warfarin requires regular blood tests for dose adjustments, and it interacts with many medications and foods. More recently, new oral anticoagulants have become available, which do not require blood monitoring, and which only have very few drug interactions. These include the direct thrombin inhibitor dabigatran [17] as well as the Factor Xa inhibitors apixaban [18] and rivaroxaban [19]. While these drugs have the advantage of fewer drug and food interactions, of obviating the need for INR-checks, and of a lower rate of intracranial haemorrhage, there are also several potential drawbacks to be considered. These drugs do not have an antidote, and bleeding in patients with overdose may be difficult to control. Activated charcoal, renal dialysis or giving factor VII are current treatment options. Furthermore, the half-life of these agents is short, allowing minor bleeds to settle spontaneously. However, in the absence of any bleeding, the short half-life could also be a disadvantage, in that patients need to comply well with their medication to get adequate protection from embolic events. Further points to consider are that the dose has to be reduced in renal impairment, and that gastro-intestinal side effects are common, with the rate of