Update on the treatment and prevention of ischaemic stroke

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Background

Stroke continues to have a devastating impact on public health. Each year approximately 15–20 million people worldwide have a new or recurrent stroke, which results in 5 million deaths. Stroke remains a leading cause of death and disability in the United States. At least 700,000 new stroke cases occur every year, approximately 85% of which are ischaemic in nature. Although the incidence of ischaemic stroke has declined over the past 20 years, the mean age of the population has risen, resulting in a continual increase in the absolute number of strokes.

Over the past 10 years, hospitalisation due to stroke has increased by about 18%. Most of this increase has been seen because of an increase in the proportion of patients with ischaemic stroke.

Recent epidemiological studies suggest that stroke is becoming more common, perhaps due to the ageing of the population and increased survival of patients with cardiac disease. The 10-year probability of having a stroke increases dramatically with age for both men and women (Figure 1). These data suggest that there is an increased need for improved methods to both prevent strokes and treat people with cerebrovascular disease.

Acute therapy

The only approved therapy for acute ischaemic stroke is intravenous tissue plasminogen activator (tPA). The disadvantage of tPA treatment is a rate of symptomatic haemorrhage of about 6%. Newer stroke prevention options are currently being investigated including statins, oestrogen, angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs). The challenge for physicians is to select the most effective intervention, and this depends on our knowledge of the underlying stroke mechanism and the patient’s risk factors.
medical or surgical therapies for intracerebral haemorrhage at the present time. The limitations of acute therapies are a major reason to emphasize prevention as a key element in the effort to reduce the effects of stroke and cerebrovascular disease.

Anticoagulation Therapy

Anticoagulation therapy, particularly with heparin or heparinoids, is another area under investigation for the treatment of stroke. A recent meta-analysis considered 21 studies encompassing over 23,000 patients who received intravenous heparin (majority of patients) and other agents. The primary endpoint of these trials was death or recurrent stroke at 2 weeks, and almost all of the patients had undergone head CT scans. The results of this meta-analysis showed that patients who did not receive anticoagulation therapy had a higher rate of recurrent ischaemic stroke and a lower rate of haemorrhage than those patients who received anticoagulation therapy. However, in the patients who did receive anticoagulation therapy, the rate of ischaemic stroke was reduced, but that was offset by an increased rate of cerebral haemorrhage, making the net benefit zero. Whether or not a patient received anticoagulation therapy, the rate of recurrent stroke, both ischaemic and haemorrhagic, was exactly the same: 4.1% at 2 weeks.

In four large prospective, randomised studies from the 21 studies in the meta-analysis (TOAST, HAEST, TAIST and FISS-bis), different low molecular weight heparins were compared with either aspirin or placebo for the treatment of stroke. The results from all four studies showed that there were no net benefits from receiving the heparinoids.

Aspirin

There are data supporting the efficacy of aspirin as an acute stroke therapy from two large studies – IST (the International Stroke Trial) and the Chinese Aspirin Stroke Trial. There was an overall net benefit of 9 to 10 (per thousand patients treated) fewer recurrent strokes and deaths when low doses of aspirin (100–300 mg/day) were started within 48 h of stroke onset and continued for at least 2 weeks. The benefits of aspirin treatment are modest, but they are statistically significant and it is recommended that all stroke patients be given aspirin.

Risk factors and stroke prevention

After an initial vascular event, such as a myocardial infarct (MI), ischaemic stroke, or peripheral arterial disease, patients are at an increased risk of having a subsequent MI (3–4 times) or subsequent stroke (9 times). Thus, if a patient has an ischaemic stroke, their highest short-term risk is to have another ischaemic stroke. In a matter of months you have about an 8–10% risk per year of having another stroke, particularly in the first year after the initial ischaemic stroke.

The most important risk factor in terms of prevalence and relative risk reduction in stroke is hypertension (Figure 2). Hypertension has a prevalence of 30–35%, and a relative risk of producing a stroke, of 3–5 times baseline. Therefore, anything that can be done to improve the treatment of hypertension would be beneficial.

There are several options that can be considered for stroke prevention. These include antiplatelet therapy, anticoagulation therapy, statin therapy, hormone replacement therapy (HRT), angiotensin converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs).

![Figure 1. Effects of age on stroke risk in men and women](image)

*Figure 1. Effects of age on stroke risk in men and women*

![Figure 2. Stroke risk factors in terms of prevalence and relative risk. HTN = hypertension](image)

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Anti-platelet Therapy

The two commonly used anti-platelet therapies are clopidogrel (Plavix, Bristol-Myers Squibb/Sanofi-Synthelabo)\(^{17}\) and dipyridamole + aspirin (Aggrenox, Boehringer Ingelheim)\(^{18}\). Clopidogrel is very well tolerated with fewer side-effects than aspirin, and is easy to use, but it is expensive. Clopidogrel has limited efficacy when used alone, although it does appear to be slightly more effective than aspirin in reducing vascular events overall\(^{17}\). Data suggest that clopidogrel may be more efficacious when used in combination with aspirin\(^{19}\) and studies investigating this combination for stroke prevention are ongoing, e.g. MATCH.

Dipyridamole + aspirin is a combination of low-dose aspirin and extended-release dipyridamole. This agent shows good efficacy for stroke prevention with a relative risk reduction of about 37%\(^{20}\). However, it has significant side-effects, including headaches and gastrointestinal intolerance, and is more expensive than aspirin. It is unclear whether dipyridamole + aspirin has benefit in patients with coronary artery disease.

The results of the WARSS study, which looked at the effect of warfarin on recurrent stroke prevention, showed no net benefit of warfarin over aspirin\(^{21}\). These results and other issues, including drug interactions, mean that warfarin is falling out of favour for stroke prevention, except for patients in atrial fibrillation.

The Antiplaetelet Trialist Collaboration (ATC) meta-analysis\(^{22}\), looked at all the antiplatelet agents together, and the benefit for 1000 patients treated over 5 years was 25 non-fatal stroke recurrences in patients who had suffered a stroke or a transient ischaemic attack. Therefore, these results leave plenty of room for improvement.

Newer pharmacological interventions for preventing stroke

Newer stroke prevention options currently being investigated include statin agents, oestrogens, ACE inhibitors and ARBs.

Statins

Many of the statins, particularly pravastatin, simvastatin and atorvastatin, show significant risk reductions for stroke. In an analysis of the Pravastatin Pooling Project\(^{23}\), which combined results from three large pravastatin studies (over 19,000 patients), there was a significant 20% relative risk reduction in the occurrence of fatal and non-fatal strokes with active treatment (40mg/day) compared with placebo.

New data concerning the efficacy of statins for stroke prevention come from the MIRACL Trial\(^{24}\), which randomised patients with acute coronary syndromes to either placebo or high dose atorvastatin (80 mg/day). The primary endpoint was MI, death, cardiac events or worsening angina. Remarkably, the investigators found a 16% relative risk reduction in the non-fatal strokes (secondary endpoint) after only 16 weeks of active therapy compared with placebo (relative risk, 0.80; 95% CI, 0.66–0.98; \(p = 0.01\)). Furthermore, at the same endpoint there was a significant 51% relative risk reduction in the occurrence of fatal or non-fatal strokes (relative risk, 0.49; 95% CI, 0.24–0.98; \(p = 0.04\)).

Hormone Replacement Therapy (HRT)

There has been considerable debate about a possible link between HRT and stroke. Early studies had suggested that either oestrogens, or oestrogens combined with progesterone, would reduce the risk of new or recurrent strokes. Two large studies, the Women’s Health Initiative\(^{25}\) and WEST Study\(^{26}\), both contradicted this belief.

The Women’s Health Initiative studied primary prevention of cardiovascular disease in women taking combination therapy (oestrogens with progesterone). The study was stopped early because of an increase in the occurrence of ischaemic stroke, as well as an increase in MI and deep vein thrombosis.

The WEST Study was a placebo-controlled study of oestrogens in secondary prevention in postmenopausal women who had suffered a stroke. In the women who received oestrogens, there was no benefit in terms of stroke reduction. An interesting result from the WEST study was the inferior outcome (either in terms of more severe stroke or higher mortality) compared with placebo in women receiving HRT and who had a recurrent stroke. Taken together, these results have discouraged many physicians from using HRT for either primary or secondary stroke prevention.

Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

The HOPE study\(^{27}\) showed a significant 32% relative risk reduction for stroke with ramipril (ACE inhibitor) compared with placebo in patients that were perceived as a high-risk population. In the PROGRESS Study\(^{28}\), which assessed perindopril (ACE inhibitor) for secondary stroke prevention, there was an approximately 28% relative risk reduction in favour of active therapy compared to placebo.
Finally, a recent clinical trial: Losartan Intervention For Endpoint reduction in hypertension study (LIFE)\(^{29}\) has shown promising results and supports the use of ARBs in preventing stroke.

**Conclusion**

Treatment options to reverse the effect of acute ischaemic stroke are limited, but are quite effective. There are specific and well-defined risk factors in patients with stroke and a variety of medical options are available. The challenge for physicians is to select the most effective intervention, and this depends on our knowledge of the underlying stroke mechanism and the patient’s risk factors.

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