Stoke: review of 2011

Stroke causes nearly 10% of all deaths worldwide and is the leading cause of neurological disability. It accounts for more than 4% of direct health-care expenditure, with an absolute cost of about $3 billion in the UK and over US$40 billion in the USA, and also has substantial indirect costs related to complications such as post-stroke dementia, depression, falls, fractures, and epilepsy. However, significant progress is being made in the prevention and treatment of stroke. Two reports in 2011 showed that stroke mortality has fallen significantly in the US and Europe over the last decade, probably due mainly to more effective prevention.

Indeed, improvements in medical therapy probably also explain the diminishing benefits of revascularisation procedures for patients with extracranial or intracranial atherosclerotic steno-occlusive disease that has been found repeatedly in 2011. Perhaps most surprising were the findings of the SAMMPRIS trial in patients with symptomatic, intracranial arterial stenosis, which is increasingly diagnosed in patients with TIA and stroke due to the more widespread availability of MR and CT angiography. Although this group was generally considered to be at very high risk of stroke, it has been uncertain whether percutaneous transluminal angioplasty and stenting was more effective in preventing recurrent stroke than medical treatment alone. The SAMMPRIS trial therefore randomised patients who had a recent TIA or stroke attributed to 70-99% stenosis of a major intracranial artery to aggressive medical management alone or aggressive medical management plus angioplasty and stenting. Enrolment was stopped early after 453 patients were recruited, because the 30-day rate of stroke or death was 14.7% in the intervention group and only 5.8% in the medical-management only group (p=0.002). Beyond 30 days, stroke in the same territory occurred in 13 patients in each group. Follow-up is ongoing but the likelihood that the cumulative risk of stroke in the medical-treatment only group will offset the difference in 30-day risk seems low.

Aspirin maintained its position as a first line antplatelet drug in secondary prevention of stroke in patients without atrial fibrillation in 2011 following publication of the results of the PERFORM trial, which compared it with a selective thromboxane-prostaglandin receptor antagonist, terutroban. 9562 patients with an ischaemic stroke in the previous three months or a TIA in the previous eight days were randomised to terutroban and 9558 to aspirin. After mean follow-up of 28 months the trial was stopped on the basis of futility, the primary endpoint having occurred in 1091 (11%) patients receiving terutroban and 1062 (11%) receiving aspirin (HR=1.02; 95% CI 0.94-1.12), without any difference in risk of major bleeding. The annual risk of recurrent stroke was again surprisingly low.

Atrial fibrillation remains the least well treated of the major risk factors for stroke, due mainly to the perceived risk of bleeding with vitamin K antagonists, the requirement for monitoring, and the potential for drug and lifestyle interactions. About 20% of TIA’s and ischaemic strokes occur in patients with atrial fibrillation (AF). Prevalence of AF increases sharply with age and is therefore increasing in line with life expectancy. Aspirin is relatively ineffective in prevention of stroke in patients with AF either alone or in combination with clopidogrel, and warfarin has been the mainstay of treatment in both primary and secondary prevention for more than two decades. Progress was made on two fronts in 2011. First, in terms of risk-stratification, the CHA2DS2-VASc score was shown to be somewhat predictive for risk of stroke and systemic embolisation than previous risk scores, particularly in identifying patients at low and intermediate risk. Second, in terms of alternative anticoagulants to warfarin, several new agents have emerged. Previously, the factor Xa inhibitor, ximelagatran, had shown promise but was abandoned in the prevention of stroke in patients with AF and to cause fewer major bleeding complications, but it was hepatotoxic and was subsequently withdrawn. In 2009, the direct thrombin inhibitor, dabigatran, was reported to have advantages over warfarin in the PROBE-design RE-LY trial in over 12000 patients, 20% of whom had a prior TIA or stroke. With a dose of 110mg twice-daily the risk of ischaemic events did not differ from that with warfarin, but there were fewer major haemorrhages. With a dose of 150mg twice-daily there were fewer ischaemic events and a similar number of major bleeds compared with warfarin. There was net clinical benefit (vascular events, stroke or systemic death) (0.5% vs. 0.7%, p=0.02) and fatal hemorrhage (0.5% vs. 0.7%, p=0.02) and fatal bleeding (0.2% vs. 0.5%, p=0.003).

In the first trial to report in 2011, ROCKET-AF’s 14264 patients with nonvalvular AF who were at increased risk for stroke were randomised, double-blind, to rivaroxaban 20mg daily vs dose-adjusted warfarin. In the intention-to-treat analysis, rivaroxaban reduced the risk of stroke or systemic embolism (2.1%/yr vs 2.4%/yr; HR=0.88, 0.74-1.03; p=0.001 for noninferiority; p=0.12 for superiority) with a lower risk of intracranial hemorrhage (0.5% vs. 0.7%, p=0.02) and fatal bleeding (0.2% vs. 0.5%, p=0.003).

In the comparable ARISTOTLE trial, 18201 patients with AF and at least one additional risk factor for stroke were randomised, double-blind, to apixaban 5mg twice-daily vs warfarin. After a median duration of follow-up of 1.8 years, the risk of stroke or systemic embolism was lower in the apixaban group (1.27% vs 1.60%; HR=0.79, 0.66-0.95; p=0.001 for noninferiority; p=0.01 for superiority), with a lower rate of major bleeding (2.13% vs 3.09%; HR=0.69, 0.60-0.80; p=0.001) and haemorrhagic stroke (0.24% vs 0.47%; 0.51, 0.35-0.75; p=0.001). Apixaban 5mg bd was also compared...
to aspirin (81-324mg daily) in 5509 patients with AF who were at increased risk for stroke but unsuitable for warfarin in the double-blind AVERROES trial.14 After a mean follow-up of 1.1 years, the trial stopped early because of benefit in favor of apixaban (stroke or systemic embolism: 1.6% vs 3.7%; HR=0.45, 0.32-0.62; p<0.001), without any excess of major bleeding (1.4% vs 1.2%, HR=1.19, 0.74-1.75) or intracranial bleeding (n=11 vs n=13).

Thus, there are now three potential alternative anticoagulants to warfarin and guidelines will need to be updated to take these recent trial results into account, along with further analyses of cost-effectiveness and subsequent reports on long-term safety.

In treatment of acute stroke, progress was made in understanding the risks and benefits of blood pressure lowering. Blood pressure is often elevated after a TIA or stroke but tends to fall spontaneously during the first few days. Ischaemic and infarcted brain cannot autoregulate blood flow and so increases in cerebral perfusion pressure can cause hyperaemia, cerebral oedema, and haemorrhagic infarction, whereas a fall in pressure may exacerbate ischaemia. The Scandinavian Candesartan Acute Stroke Trial (SCAST) trial therefore randomised patients with acute ischaemic (85%) or haemorrhagic (14%) stroke and SBP 140mmHg within 30 hours of symptom onset (average 18 hours) to candesartan (n=1017) or placebo (n=1012) for seven days, with doses increasing from 4mg on day one to 16mg on day three to seven.15 Mean blood pressure was 171/90mmHg on admission, but SBP was 140mmHg (95% CI 3-7; p=0.0001) lower and DBP was 22mmHg (1-3; p=0.001) lower in patients allocated to candesartan than in those on placebo on day seven. The composite endpoint of stroke, myocardial infarction, or vascular death occurred in 120 patients in the candesartan group and in 111 patients in the placebo group (adjusted hazard ratio 1.09, 0.84-1.41; p=0.52). Analyses of functional outcome showed a trend towards worse outcome in the candesartan group (modified Rankin scale: adjusted odds ratio 1.17, 1.00-1.38, p=0.048). The SCAST investigators added their results to a meta-analysis of nine smaller RCTs of BP-lowering drugs within the first week of acute stroke and found no evidence of a beneficial effect on functional outcome.

Progress in research to improve prevention and management of stroke was therefore significant in 2011, due mainly to the findings of large pragmatic randomised controlled trials. 

REFERENCES


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