Management of stroke

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Stroke is no respecter of social class, race, religion or creed. It is a global phenomenon. Stroke is the equivalent, in terms of incidence in the UK, of a fully laden Boeing 747 aircraft crashing every single week and killing everyone on board. It is a big problem.

The various manifestations of atherothrombosis—heart attack, unstable angina, stroke, transient ischaemic attack (TIA), and peripheral arterial disease—affect a staggering number of patients each year and account for approximately two-fifths of all deaths and almost a third of premature deaths (ie. in people under 75 years old).[1]

In the UK, stroke consumes 7% of the entire NHS budget and there are 300/100,000 new cases each year. In the USA there are 550,000 new cases a year with five million patients affected and more than 60% require residential care with costs as high as $50 billion per year. It is a huge business in the Western world. In addition, according to the World Health Organization by 2050, 80% of the world burden of stroke will be in two places—India and China—as their population ages and they adopt more Western lifestyles.

Common causes of stroke are age and male sex. Other risk factors include high blood pressure, atrial fibrillation, cigarette smoking, diabetes mellitus and high cholesterol, with the commonest modifiable risk factor being blood pressure. The take home message is that there is a linear increased risk of stroke with high blood pressure so blood pressure needs to be kept as low as possible. If we were to reduce blood pressure in the UK by a mere 5mmHg we would slash the incidence of stroke in this country by 40%. This could be done by reducing the amount of salt in two foods (such as bread and corn flakes) by 10%.

Management of stroke has become more effective in recent years with the launch of the National Stroke Strategy, the FAST initiative and also the use of Hyper Acute Stroke Units.

Antiplatelet therapy

Aspirin is the mainstay of treatment in stroke and it works across the board of atherothrombosis with a risk reduction of 25%.[2] There are three antiplatelets drugs available: aspirin, which inhibits the thromboxane A2 platelet aggregation pathway by inhibiting cyclooxygenase 2; clopidogrel, which blocks the ADP-stimulated platelet aggregation pathway by occupying the plasma membrane ADP receptor; and dipyridamole, which inhibits the cyclic AMP pathway by inhibiting phosphodiesterase enzyme.

The MATCH trial investigated whether aspirin 75mg plus clopidogrel 75mg was better than clopidogrel alone. The trial included 7599 patients with recent ischaemic stroke/

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TIA and one other risk factor. At 18 months, there was an absolute risk reduction of 0.72% in the incidence of stroke but there was major bleeding on the combination—3% a year. Use of dual antiplatelet therapy for stroke was therefore ceased over night.[3]

Oral anti-coagulation

Another trial—WASID (Warfarin–Aspirin Symptomatic Intracranial Disease)—reviewed warfarin over aspirin.[4] In this trial, 569 patients with cerebral intracranial stenosis identified by imaging were randomised to warfarin (INR 2–3) or aspirin (1300mg). Follow-up was two years but the trial was stopped prematurely as death was 9.7% on warfarin versus 4.3% on aspirin and haemorrhages were 8.3% in the warfarin group versus 3.2% in the aspirin arm. Caveats to the trial though are that the aspirin dose was very high and the INR target was only reached in two thirds of patients. It was found that if the INR was maintained at 2–3, then the event rate was only five per 100 patients in this trial. The event rate went higher with poorer INR rates.

Atrial fibrillation

Patients with atrial fibrillation have a five-fold increased risk of stroke and a two-fold increased risk of death. The number of patients with atrial fibrillation is also anticipated to increase as the world population ages. A larger proportion of the world population is now elderly than ever before, and recent estimates suggest that by 2025 there will be 1.2 billion individuals worldwide who are ≥60 years of age.[5]

What can we do about atrial fibrillation? We can give patients antiplatelets—there is a 25% reduction with aspirin.[6] Yet most healthcare physicians would prescribe warfarin as that has a risk reduction of 70%.[6] Another study noted that net clinical benefit significantly favoured warfarin in patients aged ≥75 years, suggesting that age should not be perceived as a barrier to anticoagulant prescription.[7]

The same trial also found that the benefit–risk increases with an increasing number of risk factors. Patients with atrial fibrillation and a CHADS2 score of 0 or 1 gained no benefit from warfarin; net benefit was observed only in patients with a CHADS2 score ≥2, with patients with a CHADS2 score of 4–6 deriving the greatest net clinical benefit from warfarin therapy.[7]

Although warfarin is undoubtedly effective for stroke prevention in patients with atrial fibrillation, the elderly in particular, face the risk of major haemorrhage during therapy.

In a study of warfarin in patients aged over 65 years,[8] the risk of major haemorrhage was shown to be particularly high for elderly patients. The cumulative incidence of major haemorrhage was: 13.1 per 100 person-years for those ≥80 years of age; 4.7 per 100 person-years for those <80 years of age (p=0.009). An increased risk of haemorrhage was associated with age ≥80 years; an INR of ≥4.0, although only 2% of person-time was spent in this range; and the first 90 days of warfarin therapy. Within the first year, 26% of patients aged ≥80 years stopped taking warfarin. Perceived safety issues accounted for 81% of these discontinuations. Rates of major haemorrhage and warfarin termination were highest among patients with CHADS2 scores ≥3.

Warfarin though is significantly more effective than dual antiplatelet therapy. In the ACTIVE-W trial, patients were allocated randomly to receive warfarin therapy (target INR 2.0–3.0) or clopidogrel (75mg/day) plus aspirin (75–100mg/day) and were intended to be followed for approximately two years. The trial was stopped early because of clear evidence of the superiority of warfarin therapy. Major bleeding rates were similar in both treatment groups.[9]

It was concluded that warfarin therapy is superior to clopidogrel plus aspirin for the prevention of vascular events in patients with atrial fibrillation at high risk of stroke.

Novel anticoagulants

There have been some novel anticoagulants that have been released into the market recently but currently only two have been approved. These are rivaroxaban, which is a direct factor Xa inhibitor and dabigatran, which is a direct factor IIa inhibitor.

The RE-LY trial was a randomised, phase III, single-blind, non-inferiority study of dabigatran versus warfarin. The primary efficacy was the composite of all-cause stroke or systemic embolism.[10]

Stroke or systemic embolism occurred in 183 patients receiving 110mg of dabigatran (1.53% per year), 134 patients receiving 150mg of dabigatran (1.11% per year) and 202 patients receiving warfarin (1.69% per year). Both doses of dabigatran were non-inferior to warfarin (p<0.001). The 150mg dose of dabigatran was

also superior to warfarin, but the 110mg dose was not.

Rates of haemorrhagic stroke were 0.38% per year in the warfarin group, compared with 0.12% per year in the group that received 110mg of dabigatran and 0.10% per year in the group that received 150mg of dabigatran.

Compared with the 110mg dose, administration of the 150mg dose of dabigatran reduced the risk of stroke or systemic embolism (p=0.005).

The rate of major bleeding was 3.36% per year in the warfarin group compared with 2.71% per year in the group that received 110mg of dabigatran and 3.11% per year in the group that received 150mg of dabigatran.

Rates of life-threatening bleeding, intracranial bleeding, and major or minor bleeding were higher with warfarin (1.80%, 0.74% and 18.15%, respectively) than with either the 110mg dose of dabigatran (1.22%, 0.23% and 14.62%, respectively) or the 150mg dose of dabigatran (1.45%, 0.30% and 16.42%, respectively).

There was a significantly higher rate of major gastrointestinal bleeding with dabigatran at the 150mg dose than with warfarin.

The FDA has only licensed the 150mg dose so far but the EU has licensed both doses.

Another study called ROCKET AF compared rivaroxaban with warfarin. This was a phase III, prospective, randomised, double-blind, double-dummy, active-controlled, multicentre, event-driven study.[11] It compared rivaroxaban with warfarin (titrated to INR 2–3) for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation plus either a history of stroke, TIA or systemic embolism, or at least two moderate risk factors for stroke (CHADS2 score ≥2).

The rivaroxaban dose was 20mg once daily—except for patients with moderate renal impairment (creatinine clearance 30–49 ml/min) at baseline who received a reduced dose (15mg once-daily).

In patients with atrial fibrillation, rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism. There was no significant between-group difference in the risk of major bleeding, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group.

Thrombolysis

Thrombolysis is another treatment option and aims to reverse the ischaemic penumbra.

The big problem with thrombolysis is that you can only do it within three hours, and it is only available in HASU centres. One trial—ECASS-3—investigated whether this licence limit of three hours could be extended.[12] It found that as compared with placebo, intravenous alteplase administered between three and 4.5 hours after the onset of symptoms significantly improved clinical outcomes in patients with acute ischaemic stroke but was more frequently associated with symptomatic intracranial haemorrhage.

Another trial— IST3— looked at whether the window could be further extended to six hours and use in patients over 80 years. For the types of patient recruited in IST-3, despite the early hazards of the first week, thrombolysis within six hours improved functional outcome. Benefit did not seem to be diminished in elderly patients.[13]

Conclusion

The least effective intervention in our armentarium is aspirin—in that we need to treat the most amount of patients to prevent one event. The reason we use it is that it is the cheapest. There are more effective treatments available.

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