Secondary Stroke Prevention in 2011: An Update on Available Options

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THE ARRAY OF MEDICAL INTERVENTIONS FOR secondary stroke prevention has dramatically increased in the last decade. The approach is multi-factorial and includes not only pharmacological, e.g., anti-platelets or anti-coagulants where appropriate, reductions in blood pressure, cholesterol lowering agents, but also lifestyle e.g., smoking cessation, diet, and exercise. This review will focus on these recent advances.

HYPERTENSION
Caution when treating blood pressure in the first week after stroke

Treatment of hypertension after stroke should be considered two-fold: the first week after stroke and the period after the first week. There was considerable debate about whether blood pressure should be lowered in the first week but the recent SCAST trial found that lowering of blood pressure with candesartan in the first week (mean blood pressure of 147/82 versus 152/84 on placebo, p<0.0001) neither reduced recurrent stroke nor mortality.1 In fact, functional outcomes at six months, as measured by the modified Rankin scale, appeared to be worse in candesartan-treated patients (adjusted common odds ratio of a poor outcome 1.17, p=0.048). Thus, aggressive treatment of blood pressure within the first week after stroke should be avoided.

Blood pressure is the single most important modifiable risk factor for stroke

Nevertheless, blood pressure should be lowered in the long-term. A systematic review found that chronic reduction of blood pressure in patients with prior ischemic or hemorrhagic stroke or transient ischemic attack reduced secondary stroke by 24%, nonfatal stroke by 21%, myocardial infarction by 21%, and total vascular events by 21% over a period of two to five years.2 No effect was seen on vascular or all cause mortality. The reduction in stroke was related to the difference in systolic blood pressure between treatment and control groups (P<0.002). All classes of drugs appeared to be effective except for beta blockers which did not show a difference compared with placebo.

The importance of medication selection for blood pressure lowering

Though beta blockers have been used for many years for reduction of blood pressure, multiple randomized trials show inferiority of beta blockers for stroke prevention compared with other agents. A Cochrane systematic review of 13 randomized trials including 91,561 participants found a trend towards worse outcomes with beta blockers when compared to calcium-channel blockers, renin-angiotensin system inhibitors, and thiazide diuretics.3 Another Cochrane review concluded that available studies supported first-line use of low-dose thiazide diuretics, ACE inhibitors, and calcium channel blockers but not high-dose thiazide diuretics or beta blockers.4 Among first-line agents, diuretics may be best followed by calcium channel blockers and then ACE inhibitors and angiotensin receptor blockers.5

The ideal blood pressure has yet to be defined: Studies are ongoing

The ultimate target for blood pressure reduction is uncertain. JNC7 recommends a blood pressure of less than 140/90 in most patients and less than 130/80 in diabetics and those with chronic kidney disease.6 The latter target was recently challenged by the ACCORD findings which found no difference in outcomes in diabetic patients allocated to a target of less than 120 mmHg systolic compared with those treated to less than 140 mmHg systolic.7 The SPS3 study, scheduled to have final results in 2012, will evaluate the difference in outcomes among patients with small subcortical strokes allocated to blood pressures of less than 130 mmHg systolic versus those allocated to blood pressures of 130-149 mmHg systolic with or without clopidogrel added to aspirin.8

HYPERLIPIDEMIA
Statins are beneficial in patients with ischemic stroke

The SPARCL trial (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) showed that lowering LDL (low density lipoprotein) levels reduces the risk of subsequent stroke.9 In this study, 4,371 patients with an ischemic stroke, hemorrhagic stroke, or TIA within the previous one to six months were randomized to 80 mg of atorvastatin or placebo. Important exclusion criteria in this study included a history of coronary artery disease and LDL levels that were not in the range of 100-190 mg/dL. Approximately 2% of all enrolled patients had hemorrhagic stroke as the qualifying event. As compared with patients receiving placebo, patients who were assigned to atorvastatin had a 2.2% absolute risk reduction of recurrent stroke over five years and a 3.5% absolute risk reduction in major cardiovascular events over five years. There was an increased risk of hemorrhagic stroke with atorvastatin use (2.3% over five years with atorvastatin versus 1.4% over five years with placebo). Nevertheless, the reduction in ischemic stroke events far outweighed the occurrence of hemorrhagic stroke events. The precise target for LDL reduction is uncertain however, the degree of LDL reduction correlates with the degree of reduction in recurrent stroke.10,11

Caution is advised when considering statins in patients with hemorrhagic stroke

In regards to statin treatment of patients with hemorrhagic stroke, a recent analysis suggested that the risks of continued use of statins in that population outweighed potential benefits.12 Avoiding statins yielded a life expectancy gain of 2.2 quality-adjusted life-years compared with statin use in such patients. The authors concluded that statin use should be avoided in patients with intracerebral hemorrhage.
Niacin and fibrates may not be beneficial for reducing risk of stroke

Attempts to lower triglyceride levels and increase HDL may be beneficial for patients who have had a stroke or TIA. In the Veterans Affairs HDL Intervention Trial (VA-HIT), 2,531 men with coronary artery disease were assigned to gemfibrozil 1200 mg/day or placebo. The gemfibrozil group had a reduced risk of stroke over five years compared to placebo (4.6% versus 6.0%, respectively). Similarly, in an older study among patients with coronary artery disease, niacin demonstrated a reduction in stroke over five years compared with placebo (2.3% versus 2.9%). However, recent trials targeting HDL and triglycerides have not been positive. In the AIM-HIGH trial, high-dose extended release niacin was added to simvastatin and produced the expected effect of raising HDL and lowering triglycerides, however the study stopped early because a futility analysis showed that clinical outcomes were not significantly affected. In the ACCORD lipid study, the addition of fenofibrate to simvastatin did not further reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke, as compared with simvastatin alone. Finally, in the ILLUMINATE trial, torcetrapib, an investigational agent, also raised HDL and reduced triglycerides but increased the rate of cardiovascular events.

LIFESTYLE MODIFICATION

Smoking

Both active and secondhand exposure to tobacco smoking increases the risk of stroke. The average number of quit attempts by former smokers is approximately six. Approximately 2% of patients who are counseled to stop smoking during a single office visit will do so and not relapse after one year. Nicotine replacement therapy results in 13% of patients being smoke free. At this time, there is insufficient data to support acupuncture, acupressure, laser therapy, and electrostimulation for smoking cessation. Pharmacotherapy that has been shown to increase the chances of smoking cessation include bupropion and varenicline.

Alcohol consumption

While chronic heavy alcohol use increases the risk of ischemic stroke, light to moderate consumption may be somewhat protective, though there may be a slightly increased risk of stroke immediately following alcohol consumption. Daily consumption of small amounts of alcohol, defined as one drink per day for women and two drinks per day for men, may reduce platelet aggregation and raise HDL. While patients who drink heavily should be encouraged to cut back or quit, there is insufficient evidence at this time that non-drinkers should be advised to start drinking alcohol.

Physical activity

Physical activity should be encouraged in all patients as part of both primary and secondary prevention of stroke. In terms of primary prevention, moderate degrees of exercise may reduce the risk of stroke by about 20% while high levels of activity may cut stroke risk by about 30%. Though the beneficial role of exercise in secondary prevention has not been validated through randomized clinical trials, exercise is widely held as likely in helping to improve physical disability as well as reduce the risk of further events. For patients with post-stroke disability or deconditioning, physical therapy can provide a structured environment for increasing activity appropriately. Outside of such programs, patients should be counseled to maintain as active a lifestyle as possible. Randomized clinical trials show that robotic therapy and virtual gaming are also helpful in improving physical function.

TREATMENT OF STROKE PATIENTS WITH ATRIAL FIBRILLATION

Anticoagulation in patients with stroke and atrial fibrillation should be favored, when feasible

There is robust evidence that patients with atrial fibrillation and stroke should be started on anticoagulation, if feasible. In patients with atrial fibrillation, warfarin reduces the risk of stroke by approximately 60% while antiplatelets reduce the risk by 20%. Assuming an annual recurrent event rate of approximately 10% in patients with atrial fibrillation and stroke, the absolute risk reduction is substantial.

Novel treatment options for patients with stroke and atrial fibrillation

Warfarin was first patented in 1941 as a rodenticide and approved for therapeutic use in humans in 1954. It inhibits the enzyme epoxide reductase which results in disruption of vitamin K metabolism. The most significant advance in secondary stroke prevention for atrial fibrillation in the last year was the introduction of a monitoring-free alternative to warfarin. Dabigatran is a competitive direct thrombin inhibitor which prevents the conversion of fibrinogen to fibrin. Previously available in Europe and Canada for the prevention of deep vein thrombosis in orthopedic surgery patients, dabigatran was approved for use based on results of the Re-LY (Randomized Evaluation of Long term anticoagulant therapy) trial.

The RE-LY trial compared the efficacy and safety of open-label adjusted-dose warfarin (goal INR of 2 to 3), versus fixed-dose dabigatran high (either 150mg twice daily or 110 mg twice daily). 18,113 patients with a history of both atrial fibrillation and at least one additional stroke risk factor were randomly assigned to one of the three treatment arms. The concomitant use of anti-platelet agents such as aspirin or clopidogrel was permitted. The primary outcome in the trial was the time to clinically evident stroke or systemic embolism, including pulmonary embolism and myocardial infarction.

At entry, the mean CHADS2 score was 2.1. While both the 110mg and 150mg twice daily doses of dabigatran were found to be non-inferior to warfarin for prevention of stroke, the 150mg twice daily dose was, in fact, superior to warfarin. Patients randomized to warfarin had at 1.69% per year rate of the primary study outcome of stroke or embolism, as compared to 1.11% per year for patients randomized to 150mg of dabigatran. Patients in the adjusted-dose warfarin arm were in the target range (INR 2-3) 64% of the time. A post-hoc analysis indicated that dabigatran 150 mg twice daily was superior to warfarin regardless of percentage time in the therapeutic range. Patients in the warfarin arm had a rate of major bleeding events of 3.36% per year, with a hemorrhagic stroke rate of 0.38% per year, while patients receiving dabigatran 110 mg twice daily had a major bleeding rate of 2.71% and hemorrhagic stroke rate of 0.12%. Patients receiving dabigatran 150 mg twice daily had major...
bleeding rates of 3.11% and hemorrhagic stroke rate of 0.10% per year.

In October 2010, the FDA advisory board approved the 150mg dose of dabigatran. However, the FDA did not approve the 110 mg dose because their analysis failed to show a group for whom this dose would be beneficial.37 The main point of the decision was that major bleeding which was not intracranial was not weighted as important as stroke.

There is no known reversal agent for dabigatran if a patient does experience hemorrhage. The medication should be stopped if bleeding occurs. Other interventions such as fresh frozen plasma and other coagulation factor concentrates are of uncertain utility.

For patients presenting with acute ischemic stroke in whom tPA is being considered, there is one case report of a patient who was treated seven hours after last ingestion of dabigatran without subsequent hemorrhage.38 Because the half-life is 12-17 hours, patients may be considered for treatment 12-24 hours after the last dose although no large scale studies are available at this time.

If a patient is transitioned from warfarin to dabigatran, the recommendation is to wait until the INR is below 2.0 before starting dabigatran. Dabigatran's onset of action is one hour after ingestion. Although no monitoring is required for patients taking dabigatran, its effect can be determined by testing an ecarin clotting time (ECT) or a thrombin time (TT). Both the ECT and TT have linear results with respect to dabigatran plasma concentrations. The activated partial thromboplastin time (aPTT) can also be used although its correlation with dabigatran levels is nonlinear. The INR should be used since it is unaffected by dabigatran.

In regards to clearance for surgery and other procedures, the manufacturer’s prescribing information suggests that for most patients with normal creatinine clearance, stopping dabigatran one to two days prior to most invasive procedures is appropriate; three to five days for patient with reduced creatinine clearance may be required. Dabigatran should be restarted post-procedure as soon as clinically possible. Dabigatran cannot be crushed and given via naso-gastric tube.

Though dabigatran use is cost-effective from a societal perspective (reference), at an individual level, it is more expensive than warfarin (cost comparison on drugstore.com). For patients who are stable on warfarin, the recommendation is to maintain warfarin treatment.

One final note concerns the packaging of dabigatran. Given in blister packs (which is common in Europe), the drug is useful for at least one year. However, when administered as pills in a bottle (which is common in the United States), exposure to air results in rapid deterioration of the drug such that it may not be effective after 30-90 days. We recommend that the medication be prescribed in blister packs for this reason. Most pharmacies are able to accommodate this request.

Other direct thrombin inhibitors

Two other direct thrombin inhibitors are under consideration by the FDA at the time of this writing. The Rocket-AF trial showed non-inferiority of the Factor Xa inhibitor rivaroxaban when compared to warfarin in the prevention of stroke in patients with atrial fibrillation.39 An on-treatment analysis showed a 21% reduction in the risk of stroke and non-CNS embolic events, though an intention-to-treat analysis failed to show superiority of the drug. Bleeding rates were found to be statistically equivalent between the two drugs. The AVERROES trial showed that apixaban was superior to aspirin for the prevention of stroke (1.6% per year versus 3.7% per year) in patients who were unwilling to take warfarin in the setting of atrial fibrillation or were deemed unsuitable.40

Alternative strategies for patients with stroke and atrial fibrillation who cannot be anticoagulated

The Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE-W) which compared the use of warfarin with INR 2.0-3.0 to aspirin 75-100 mg plus clopidogrel 75 mg was stopped early because the rate of ischemic stroke was substantially higher in the combination antiplatelet group (5.60% per year versus 3.93% per year).41 Therefore patients who have atrial fibrillation and are candidates for anticoagulation should preferentially receive warfarin or a direct thrombin inhibitor.

Some patients are deemed unsuitable for anticoagulation for a number of reasons including frequent falls. For these patients, the ACTIVE-A trial showed that the combination of clopidogrel plus aspirin was mildly superior to aspirin alone for reducing the occurrence of stroke (2.4% per year versus 3.3% per year).42 The risk of major bleeding was higher when clopidogrel was added to aspirin (2.0% per year versus 1.3% per year).

Other antiplatelet agents

In the Cilostazol Stroke Prevention Study 2 (CSPS-2), cilostazol appeared to be more effective than aspirin in preventing recurrent stroke (yearly rate of 2.76% versus 3.71%) with a lower rate of hemorrhage (0.77% versus 1.78%).43 It has not been FDA approved for this purpose yet, and may not be approved at all because the study took place outside the United States (in Japan).

The hazards of long-term dual antiplatelet therapy

An increased risk of bleeding with dual antiplatelet therapy was found in The Management of ATherothrombosis with Clopidogrel in High-risk patients with recent TIA or ischemic stroke (MATCH) study which showed that the addition of aspirin to clopidogrel had no net benefit in preventing stroke over clopidogrel alone but greatly increased the risk of bleeding.44 Likewise, in the CHARISMA study,45 the combination of aspirin and clopidogrel had no advantage over aspirin monotherapy for the prevention of cardiovascular events, but did increase the risk of bleeding. Taken together, these studies indicate that monotherapy should be the treatment of choice for long-term secondary prevention in patients with non-atrial fibrillation stroke.

Though the MATCH trial showed no benefit of dual anti-platelet therapy over clopidogrel alone over the long term, the role for short term combination therapy following stroke is still under investigation.

The ongoing Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trial is comparing clopidogrel plus aspirin versus aspirin alone for 90 days following stroke.46

Conclusion and future directions

Though stroke continues to be common, advances in medical treatment have substantially reduced the risk of recurrence. Using a strategy of blood pressure