Juggling the Options for Secondary Stroke Prevention

With new research challenging long-held treatment principles, standards of care are up in the air. Here's how to stay on the ball.

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Let's face it—a discussion about secondary stroke prevention just isn't sexy. When you are dealing with the realm of stroke care, acute stroke prevention is the sexy topic while stroke prevention is, well, boring. With acute intervention, you get to rush to the bedside of an acutely ill patient. You get to order the latest fancy diagnostic imaging techniques and neuroradiologic interventions. And if your intervention works, the patient gets up off the stretcher, walks out of the hospital and is eternally grateful to you for saving his life.

With secondary stroke prevention, by contrast, you see a stable patient. You give them expensive drugs that may make them feel worse because of side effects. And the best you can hope for is that the patient, after years of treatment, will feel no worse. No dramatic improvement. No patient who is eternally grateful. So, why is this important? Because the best acute stroke intervention we have, IV tPA, requires that we treat eight patients to get one good outcome. Clearly, in 2007 the best treatment for our patients is to keep them out of the emergency room in the first place. The only way to do that is to optimize stroke prevention with an evidence-based strategy.

The main thrust of stroke prevention hasn't really changed over the last 20 years. We need to use antithrombotics, mechanically reopen partially blocked arteries in appropriately-selected patients, and lower risk factors. But new research has called into question some of the tactics we use to achieve these strategies. What have we learned recently that has altered our approach?

Choosing an Antiplatelet Agent

The British Antiplatelet Trialists, in 2002, published a meta-analysis of all antiplatelet trials that convincingly showed that antiplatelet agents make a statistically significant and clinically important contribution to secondary stroke prevention.[1] The mainstay of antiplatelet agents has been aspirin. What have we learned since 2002?

The approved antiplatelet agents for stroke prevention include aspirin, ticlopidine, clopidogrel and the combination of aspirin and extended-release dipyridamole. While the original TASS study[2] suggested a benefit for ticlopidine over aspirin, the more recent AAASPS trial[3] cast doubt about the benefit of ticlopidine over aspirin. The side effect profile for ticlopidine, including frequent gastrointestinal problems, less common but potentially life threatening neutropenia, and rare but potentially lethal thrombotic thrombocytopenia purpura, made it difficult to use and a poor overall choice for stroke prevention.

The CAPRIE trial[4] tested clopidogrel against aspirin in patients with prior myocardial infarction (MI), stroke, or peripheral vascular disease (PVD). The results suggest a slight, but statistically significant, advantage for clopidogrel for the primary endpoint of MI, stroke and death. The side-effect profile was slightly better than aspirin for gastrointestinal bleeding and, with once a day dosing, it was easy to use.

The combination of aspirin and dipyridamole had been tested in several smaller trials in the 1980s. Each failed to show benefit for the combination over aspirin alone. In the 1990s, a large trial, ESPS2, reported a significant benefit for the combination of extended-release dipyridamole plus aspirin versus aspirin alone in a population at high risk for stroke. For numerous reasons, the results of this trial were not widely accepted and there were calls for a second trial to verify these results.[5,6]

What's new: Data from stent trials suggested that the combination of aspirin plus clopidogrel could improve the antiplatelet effect and potentially improve outcomes. Two trials have now reported results of this combination in a stroke population. The MATCH trial[7] entered 7599 patients with a stroke or transient ischemic attack (TIA) in the last 30 days plus at least one other vascular risk factor. Patients were randomized to aspirin plus clopidogrel or clopidogrel alone. The primary endpoint was stroke, MI, vascular death, or re-hospitalization for an ischemic event. The authors reported no benefit in terms of the primary endpoint. Secondary analysis found no benefit in terms of reduction of stroke as an endpoint. However, there was a statistically significant and clinically important increase in both major bleeding and life threatening bleeding.

The CHARISMA trial[8] entered 15,603 patients with symptomatic coronary artery disease (CAD), cerebrovascular disease, PVD, or multiple atherosclerotic risk factors. Patients were randomized to aspirin plus clopidogrel or aspirin alone. The primary endpoint was MI, stroke or death. The authors reported no benefit for combination therapy over aspirin alone. However, the combination was again reported to have a statistically significant and clinically important increased risk of bleeding complications.

A decade after ESPS2, a second trial comparing aspirin plus dipyridamole (83 percent using an extended-release formulation) versus aspirin alone for secondary stroke prevention, ESPRIT, reported its results.[9] They randomized 2739 patients at high risk for stroke and followed them for a mean of 3.5 years. The primary endpoint was vascular death, stroke, MI or major bleed. The authors reported a significant decrease in the primary endpoint for the combination of aspirin plus ER dipyridamole (13 vs. 16 percent) without an increase in bleeding complications.

Using an Anticoagulant

Is there a role for anticoagulation in non-cardioembolic stroke prevention? There are two prospective randomized trials that tested this hypothesis. The Stroke Prevention in Reversible Ischemia Trial (SPIRIT)[10] tested high dose anticoagulation (target INR 3.0-4.5) versus aspirin for secondary stroke prevention. The trial was terminated early because of the high rate of bleeding complications in the anticoagulation arm. The WARSS trial compared warfarin (target INR 1.4-2.8) to aspirin for secondary stroke prevention in patients with no cardioembolic source and without significant carotid stenosis. They found that warfarin was no more effective than aspirin in preventing stroke or the combination of stroke and death.

What's new: The results of the WARSS trial left open the possible role for warfarin in patients with symptomatic intracranial stenosis. A retrospective study demonstrated a potential benefit for warfarin in this high-risk population. This hypothesis was tested in the prospective randomized WASID trial. In 2005, the WASID trial[11] reported an increased risk for warfarin with no benefit for warfarin over aspirin in this population.

It was hoped that a new, more convenient and safer anticoagulant could be developed to replace warfarin. The results of the SPORTIF III and SPORTIF V trials led to the hope that ximelagatran could be that agent.[12] Unfortunately, because of problems with liver enzyme abnormalities and increased rate of coronary artery disease, the FDA did not approve the drug.[13]

Applying the new data: Using data from the recent trials, we can now answer the questions regarding antithrombotics for stroke prevention in non-cardioembolic stroke: is there a benefit for any given drug in terms of efficacy, side effect profile and cost? A synopsis of the data is presented in Table 1. The only drug with a proven efficacy advantage over aspirin alone is the combination of aspirin plus extended-release dipyridamole. While it has a low side effect profile comparable to aspirin, the cost is very high. For patients where cost is not the major factor in choosing a drug, this combination is a reasonable first choice for secondary stroke prevention.

For most patients, the combination of clopidogrel plus aspirin has no efficacy advantage over aspirin alone in secondary stroke prevention, but comes with an unacceptable high risk of bleeding and a very high cost. For secondary stroke prevention, this combination is not a reasonable first choice for most patients. This combination should be considered for stroke patients with a recent acute coronary syndrome or recent placement of a stent. Clopidogrel as a single agent has an efficacy and side-effect profile comparable to aspirin. Because of its cost, for most patients it is not a reasonable first choice over aspirin. However, it is the drug of choice in patients who are unable to tolerate aspirin. Warfarin is neither safer nor more effective than aspirin for secondary prevention in the overwhelming majority of non-cardioembolic strokes. It is also not a reasonable first choice as a "rescue" drug for aspirin failures.

Choosing an Approach to Stenosis

In the late 1980s and early 1990s there were six major prospective randomized trials that changed the approach to the stenotic carotid artery. Three dealt with carotid endarterectomy (CEA) for asymptomatic stenosis (VA Coop Study 167, ACAS and ACST).[14-16] While the design for each study was somewhat different, especially in terms of endpoints, each demonstrated a small benefit in favor of CEA when the surgery was performed with an operative stroke and death complication rate less than three percent. With the low procedure-related complication rate, the number needed to treat to prevent one ipsilateral stroke or operative death in five years is approximately 20.

Three prospective randomized trials that dealt with CEA for symptomatic stenosis (NASCET, ECST, and VA Coop Study 309).[17-19] A meta-analysis of data from the symptomatic trials demonstrated a very significant benefit in favor of CEA over medical management to prevent ipsilateral stroke or perioperative death for high grade stenosis ≥70 percent (excluding near occlusion) with a number needed to treat of six.[20] For 50 to 69 percent stenosis, the benefit was much less impressive but still statistically significant with the number needed to treat of 22 to prevent one stroke in five years. To achieve even this modest benefit, the procedure related complication must be ≤ six percent.

For lesser degrees of stenosis, CEA was either of no benefit or harmful. Pooled data from the NASCET and ECST demonstrated that timing of CEA after symptoms and gender make a large difference in outcomes.[21] For patients with 70 to 99 percent stenosis, maximum benefit was achieved when the surgery was performed within two weeks of symptoms. For patients with 50 to 69 percent stenosis, all benefit was lost when the surgery was performed more than two weeks after the symptoms. When segregated by gender, no benefit was found for women, even with high-grade stenosis, when the procedure was done more than two weeks after symptoms.

The newer alternative to CEA is carotid angioplasty and stenting (CAS). I am aware of just six prospective randomized trials comparing CAS to CEA. The initial trial was stopped after just

17 patients were randomized because of the high complication rate in the CAS arm.[22] The WALLSTENT trial was also stopped early because of excessive complications in the CAS arm.[23] The CAVATAS trial found no difference in post-procedure complication rates between CAS and CEA.[24] However, a difficulty in interpreting the CAVATAS data is the very high rate of post-CEA complications, 9.9 percent stroke or death at 30 days, compared to NASCET and ECST, especially considering similar patient populations.

The SAPPHIRE trial was an industry-sponsored trial that randomized 307 patients to CEA or CAS procedures. The patients had to have one or more moderate to severe co-morbidities. They found significantly fewer primary endpoints (stroke, MI and death) in the CAS group at 30 days (5.8 vs. 12.6 percent). However, the study randomized only 87 symptomatic patients. The 30-day post-CEA stroke and death rate was 10.3 percent in this high-risk group of patients. At the two-year follow up, the stroke rate for the combined group of asymptomatic and symptomatic patients was 5.8 percent for the CEA group and 5.6 percent for the CAS group. Because of the small number of symptomatic patients randomized, many felt that more data is needed prior to adopting this form of therapy over the "tried and true" CEA.

What's new: The endarterectomy versus stenting in patients with symptomatic severe stenosis (EVA-3S) trial was a French publicly-funded trial that reported their results in 2006.[25] After the first 80 patients were randomized, the data safety monitoring committee required that a cerebral protection device be used in the CAS arm of the trial. The trial was stopped after 527 patients were randomized for reasons of both safety and futility. Their 30-day stroke or death rate was 3.9 percent for CEA and 9.6 percent for CAS (p=0.01). At six months, the risk of any stroke or death was 6.1 percent for CEA and 11.7 for CAS (p=0.02).

The stent supported percutaneous angioplasty of the carotid artery vs. endarterectomy (SPACE) trial also reported results last year.[26] The 30-day ipsilateral stroke or death rate for the CEA arm was 6.3 percent compared to 6.8 percent for the CAS arm. They were unable to demonstrate non-inferiority of CAS.

Applying the new data: Based on the data available to date for CAS, until more data are available from high quality, prospective, randomized trials (*e.g.*, CREST, ICSS), I feel the only role for CAS is in symptomatic patients with ≥70 percent stenosis who have failed medical management and are not candidates for a CEA.

Choosing an Antihypertensive Strategy

Evidence from prospective cohort studies demonstrated that, for all age brackets, the risk of stroke increased with increasing systolic blood pressure.[27] A systolic pressure >115mm Hg explains 60 percent of the population-attributable risk of stroke.[28]

Table 1. Comparison of Antithrombotic Agents for Secondary Stroke Prevention

Based on indirect comparisons in prospective randomized trials

Agent	*Efficacy*	*Side Effects*	*Cost*
ASA	+	Low	Very low
Ticlopidine	+	High	Moderate
Clopidogrel	+	Low	High
Clopidogrel + ASA	+	High	High
ER-DP + ASA	++	Low	High
Warfarin	+	Low	Moderate

It is recommended that non-diabetics maintain a systolic pressure below 140 and diabetics below 130.[29] The HOPE trial reported improved stroke prevention by 31 percent using an ACE inhibitor compared to placebo, well out of proportion to the expected result in view of a blood pressure drop of only 3/2mm Hg.[30]

The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) studied antihypertensive medications in a secondary stroke prevention trial. It enrolled 6105 patients with a history of stroke or transient ischemic attack (TIA) within five years of randomization. Patients were randomized to receive placebo or perindopril with or without indapamide (added at the treating doctor's discretion) and were followed for four years.[31] The authors reported a 28 percent relative risk reduction for stroke in the treatment arm, with a 43 percent risk reduction for those patients on both the ACE inhibitor and the thiazide diuretic.

In the Losartan Intervention for Endpoint Reduction (LIFE) trial, addressing primary prevention, 9193 hypertensive patients were randomized to receive an ARB, losartan, or a beta blocker, atenolol. The group receiving the ARB had a 25 percent reduction in the rate of stroke despite comparable amount of blood pressure control.[32] The largest trial, ALLHAT, randomized 33,357 hypertensive patients, who had one additional risk factor, to treatment with chlorthalidone, amlodipine, or lisinopril. After 4.9 years follow up, they found no difference for the primary end point. In a head to head comparison with stroke as an endpoint, chlorthalidone had a relative risk reduction of 15 percent compared to lisinopril.

What's new: In the MOSES trial, 1404 hypertensive stroke survivors were randomized to BP control using an ARB (eprosartan) or a calcium channel blocker (nitendipine). Comparable levels of blood pressure control was achieved in both groups. The eprosartan group had a significantly decreased rate of primary endpoints (mortality, cardiovascular events and cerebrovascular

events). In a meta-regression analysis of trials comparing CCBs or ACE inhibitors with placebo, the authors found that blood pressure control is fundamental to decreasing the risk of stroke.[33] They concluded that over and beyond the blood pressure reduction, CCBs appear superior to ACE inhibitors for prevention of stroke, suggesting that CCBs may be especially indicated in high risk populations for stroke such as Asians or older patients with isolated hypertension.[34]

Applying the new data: While there seems to be conflicting data regarding which antihypertensive agent to use as a first line agent for optimal secondary stroke prevention, it is clear that blood pressure control is critical. Since most of my patients require more than one agent to get satisfactory control, using some combination of diuretic, CCB, ACE inhibitors and/or ARB seems reasonable. Data from our group and others demonstrated that blood pressure control is less than ideal just one year after a stroke.[35] Neurologists need to take a leadership role of blood pressure management after their patient has a stroke to ensure appropriate levels of control, beginning early after the stroke and continuing on a long-term basis.

Choosing a Strategy for Hyperlipidemia

Data from multiple clinical trials demonstrated that hyperlipidemia is a significant risk for vascular disease and that cholesterol lowering therapy lowers vascular risk in patients with cardiovascular disease. The National Cholesterol Education Program Adult Treatment Panel III (ATP III) guidelines, published in 2004, recommend a low-density lipoprotein cholesterol (LDL-C) of <70 mg/dL in very high-risk patients as a reasonable strategy.[36] They recommended that for the high-risk patient that has high triglycerides or low high-density lipoprotein cholesterol (HDL-C), consideration can be given to combining a fibrate or nicotinic acid with an LDL-lowering drug.

What's new: The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) investigators randomized 4731 patients who had recent TIA or stroke but no known coronary disease and an LDL-C between 100 and 190mg/dL.[37] Patients were randomized to atorvastatin 80mg or placebo and followed for 4.9 years. For the atorvastatin group, the mean LDL-C was 73mg/dL while the placebo treated patients had a mean LDL-C of 129mg/dL. There were 11.2 percent strokes (9.2 percent ischemic stroke) in the atorvastatin group while the placebo arm had 13.1 percent (11.6 percent ischemic stroke). The absolute risk reduction for major cardiovascular events was 3.5 percent. This means approximately 29 patients would need to be treated for five years to prevent one major cardiovascular event.

Applying the new data: Data on use of statins for secondary stroke prevention from prior studies were mixed. The Heart Protection Study reported a subset of patients that entered the study with prior stroke.[38] There was no benefit in secondary stroke prevention in those patients. However, the Heart Protection Study entered patients over four years after the index stroke. SPARCL was the first secondary stroke prevention trial. Patients were entered from one to six months after the index stroke. This most closely replicates the setting in which I see patients after a stroke. For the stroke patients who carry multiple other risk factors and have no contraindication to statin therapy, I start the patient on a statin with a target LDL-C of 70 mg/dL. For the occasional stroke patient who does not carry multiple other risk factors, I will start a statin with a target LDL-C of <100mg/dL.

Choosing a Strategy for Glucose Control

Diabetes is a major risk factor for vascular disease in general and, specifically, for stroke.[39] Patients with diabetes have between two to six times higher risk of having a stroke.[40] Aggressive risk factor management can reduce the risk of first stroke in diabetic patients.[41] Recent guidelines stress aggressive risk factor management with an ACE inhibitor or ARB plus a statin for primary prevention of stroke.

What's new: The PROactive study randomized 5238 patients with Type 2 diabetes plus a history of macrovascular disease to pioglitazone or placebo in addition to current diabetes and cardiac medications.[42] In the 984 patients entering the trial with a prior stoke, those treated with pioglitazone had a significantly reduced rate of fatal or nonfatal stroke (5.6 vs. 10.2 percent) and cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (13.0 vs. 17.7 percent). There was no effect on first stroke in this study.

Applying the new data: Stroke survivors with Type 2 diabetes require rigorous management of their diabetes, especially hypertension and lipids. While the PROactive trial was a large, well done prospective trial, the results have not been validated by a second trial. Proglitazone is an approved drug for use in diabetic patients. In patients with no contraindication, I feel it is reasonable to consider adding this drug to the existing regimen for enhanced secondary stroke prevention. There is an on-going trial, Insulin Resistance Intervention after Stroke Trial (IRIS), testing whether pioglitazone is effective in secondary stroke prevention in patients with insulin resistance. **PN**

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