Stroke Prevention:
What's the Secret?

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I have yet to meet a patient over 70 who did not agree with the proposition that death would be preferable to a bad stroke. Because the risk of stroke increases steeply with age, and our population is aging quickly, a huge increase in stroke has been forecast by the Heart & Stroke Foundation: a 32% increase between 1996 and 2006, and a doubling by 2006 (Figure 1).

We can prevent about 75% of strokes that would be expected in high-risk patients. Apart from the human consequences for both patients and their families, the economics are compelling. The Ontario Coordinated Stroke Strategy received estimates that doubling the proportion of patients who get tissue plasminogen activator (tPA) for acute stroke would save $50 million over five years. In the same timeframe, preventing 25% of strokes would save the province $541 million.

Effective stroke prevention includes a broad range of measures (Table 1).

Smoking cessation: Too important to ignore

The importance of smoking as a vascular risk factor is underestimated when non-smokers are compared with smokers, without distinguishing between non-smokers exposed to passive smoke on a regular basis, and those who are not. When Bonita et al carefully separated these groups, it became apparent that smoking increases stroke six-fold, and regular passive smoking at home or at work increases the risk of stroke 1.8-fold.[1] Patients with transient ischemic attack (TIA) have a 30% three-year risk of stroke; they simply cannot afford to multiply that risk by six.

I tell patients the parable of the cold lake: it doesn't take will power to go into a cold lake if one of their grandchildren is drowning, it just has to be done. The physical cravings can be reduced substantially by using a combination of nicotine patch and bupropion.[2] The nicotine patch for six weeks is much safer than continuing to smoke.

Hypertension: It's easy once you know how

The key is getting blood pressure (BP) controlled. BP control is a huge missed opportunity. Good control can reduce stroke by half,[3] but the latest Canadian data show that only 16% of patients with hypertension are well-controlled.[4]

I expect that, in part, poor BP control may be due to misplaced good will on the part of the physicians—they don't want their elderly patients to feel unwell by prescribing antihypertensive drugs.[5] However, this is a big mistake. With the exception of the rare patient with

Table 1
The major opportunities in stroke prevention

Intervention	Reduction in stroke
Smoking cessation	50% in 6 months
Diet	60% in 4 years
Blood pressure control	40-50% in 5-10 years
Appropriate endarterectomy	60% in 2 years
Anticoagulation	50% in atrial fibrillation
Antiplatelet agents	25-30% in 4 years
Lipid-lowering agents	30% in 4 years
Homocysteine treatment with vitamins	?

Using these measures can reduce risk by about 75-80% in high-risk patients.

Table 2
Sorting out resistant hypertension

	Primary hyperaldosteronism (mostly hyperplasia; rarely Conn's syndrome)	Liddle's syndrome; sodium channel mutations	Renal or renovascular hypertension
Renin	Low	Low	High
Aldosterone	High	Low	High
Primary Prescription	Spironolactone, eplerenone (Amiloride)	Amiloride	Angiotensin receptor blockers, revascularization

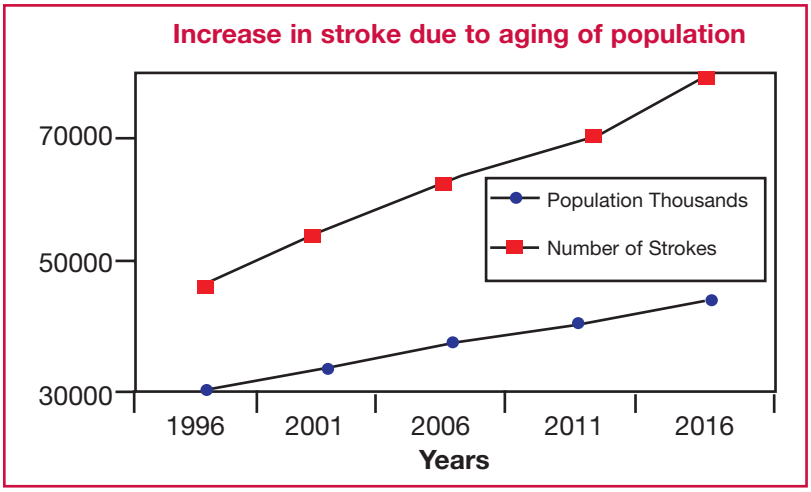

Figure 1. The impending crisis in stroke. Projections by the Ontario Heart & Stroke Foundation, 1998.

pseudohypertension, elderly patients actually feel better with good BP control,[6] and it not only reduces stroke, but also reduces Alzheimer's dementia by half.[7] Leaving elderly patients' pressure poorly controlled is not doing them a favour.

It is increasingly clear that BP targets need to be lower, especially for high-risk patients. Vasan et al. showed patients with high normal pressures have much worse vascular outcomes than do patients with ideal pressures.[8] The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) trial[9] showed a 30% reduction of stroke with perindopril and indapamide, even among patients with normal BPs.

In patients with resistant hypertension, it is necessary to define what the physiologic drivers of the BP are in the individual patient. The easiest way to do this is to measure the plasma renin and aldosterone, preferably in a stimulated condition (*i.e.,* while the patient is taking diuretics, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers).

Virtually all patients with resistant hypertension have hyperaldosteronism. It is necessary to sort out whether this is primary or secondary. It's no use saying you will leave it to the specialists because most of them don't do this sorting. It's up to family doctors to learn how to do it, the easy way. Once rare things are excluded, such as pheochromocytoma, licorice, or coarctation, there are two main types of hypertension: low renin or high renin. Low renin hypertension is caused by fluid retention, which feeds back to shut down renin. Among patients with low renin hypertension, there are two types: primary hyperaldosteronism, in which the renin is low and the aldosterone is high, and Liddle's syndrome, in which both renin and aldosterone production are suppressed. Patients with African ancestors are much more likely to have low renin hypertension.

The primary treatment for primary hyperaldosteronism is an aldosterone antagonist: spironolactone is fine for women, but men get gynecomastia from it. Eplerenone, which can be taken by either sex, should be available soon. In the meantime, amiloride can be taken by men. For Liddle's syndrome, or the new mutation that

accounts for 5% of hypertension in blacks,[10] the specific treatment is amiloride. Table 2 summarizes how the levels of renin and aldosterone sort out what physiologic disorder is driving the BP, and the primary treatment for each type of hypertension.[11] Renovascular hypertension is particularly common in the elderly, and sometimes requires revascularization.[12]

Diet: Much more important than you think

A misplaced focus on fasting lipids has led most physicians to underestimate the importance of diet.[13] The thinking goes like this: diet only reduces fasting low-density lipoprotein (LDL) by 10%, while statins can reduce it by 50%, so why bother with diet? Nothing could be further from the truth. The fasting lipids are like a baseline that affect the artery lining for the last few hours of the night. A high-fat meal affects endothelial function for four hours; from breakfast on, for the next 18 hours or so, what is affecting the artery lining is not fasting lipids, but post-prandial fat. These fats are not cholesterol, triglycerides and high-density lipoprotein, but a toxic soup of free radicals, trans fats, and other substances we don't routinely measure, so they are invisible. In a way, post-prandial fat is analogous to the two-hour post-prandial conditions (pc) blood sugar, but harder to measure.

Two important studies have shown that a Mediterranean diet reduced myocardial infarction, stroke and death by 60% in four years (the Lyon Diet Heart Study) or by 50% in two years (the Indo-Mediterranean Diet Study), compared to the diet that is routinely prescribed in our coronary care units. In the latter study, the daily cholesterol intake in the Mediterranean group was only 125 mg, so one egg yolk contains three days worth of cholesterol. Dietary cholesterol is harmful. Although an egg yolk only raises ordinary LDL by 10%, it raises oxidized LDL by 34%.[14] In patients with diabetes, an egg yolk per day doubled coronary risk compared to less than one a week.[15]

For patients with vascular disease, it is important to reduce intake of cholesterol and animal fat, while increasing the intake of olive oil, canola oil margarine, fruits, and vegetables. Instead of eggs, patients can use egg substitutes. Furthermore the daily intake of animal flesh should be reduced.[13]

What do you do for symptomatic severe stenosis?

The North American Symptomatic Carotid Endarterectomy Trial (NASCET)[16] showed that in patients with symptomatic, severe stenosis, carotid endarterectomy reduced stroke and death in two years from 26% to 9%. This trial was based on a surgical morbidity and mortality of 6%. The Asymptomatic Carotid Artery Surgery (ACAS) trial[17] showed a five-year reduction in risk from 10% to 5%, but this study was based on a very low surgical risk of 3%. When the 4.3% surgical risk observed for asymptomatic carotid stenosis patients in the Aspirin for Carotid Endarterectomy (ACE) trial is superimposed on the ACAS results, there is no longer any benefit of endarterectomy, and in the real world, the risk is at least that high.[18] The Canadian consensus recommendation is that endarterectomy should not be performed routinely for patients with asymptomatic stenosis.[19] The challenge then is to identify which asymptomatic patients may benefit. One promising approach appears to be detection of unstable plaque by the presence of microemboli on transcranial

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Table 3
Investigating the cause of ASA failure

Investigation	Finding	Specific treatment
Carotid ultrasound	Symptomatic severe stenosis	Endarterectomy
MRI	Basilar occlusion/stenosis	Anticoagulate
ECG/ECHO/Holter	AF, other cardiac source	Anticoagulate
ESR, anti-nuclear antibody	Giant cell arteritis, SLE	Prednisone, immunosuppressants, *etc.*
TCD, MRI	Intracranial stenosis	Anticoagulate
TCD bubble study	Right-to left shunt	Anticoagulate, closure of PFO or pulmonary AV fistula
TEE, MRI	Aortic atheroma	Aggressive medical prescription, anticoagulate, surgery

MRI: Magnetic resonance imaging
ECG: Electrocardiography
ESR: Erythrocyte sedimentation rate
TCD: Transcranial Doppler
TEE: Transesophageal echocardiography
PFO: Patent foramen ovale
SLE: Systemic lupus erythematosus
AF: Atrial fibrillation
AV: Atrioventricular
ECHO: Echocardiography

Take-home message

Stroke is expected to increase dramatically in Canada. As we don't have the beds now to look after all the stroke patients that are expected, our best way out of this disaster is prevention.

Effective, intensive treatment includes:

- Smoking cessation
- Blood pressure control
- Diet
- Endarterectomy in appropriate cases
- Antiplatelet agents
- Anticoagulants in appropriate cases

These measures can reduce stroke by about 75% in high-risk patients.

Doppler,[20] which identifies a subgroup at higher risk.[21] Based on current evidence, there is not the slightest chance that carotid stenting will help patients with asymptomatic stenosis.[22]

Antiplatelet agents: Not a panacea

Perhaps the most common mistake I see in emergency departments is the doubling of the dose of acetylsalicylic acid (ASA) when someone already taking ASA has a TIA. Based on the pharmacology of ASA, this approach would be predicted to be wrong, since higher doses are no more effective at reducing platelet thromboxane, but will inhibit endothelial production of beneficial prostacycline. In patients going for endarterectomy, lower doses were shown to be better at reducing risk than were high doses of ASA.[23] It is more effective to add another antiplatelet agent with a different mechanism of action, such as clopidogrel or dipyridamole.

However, it must be understood that antiplatelet agents have a limited capacity to prevent stroke, since they will only prevent strokes due to embolization of platelet aggregates (white thrombus). It takes an endarterectomy to prevent embolization of atheromatous debris. Even the best antiplatelet combinations could only prevent about 30% of stroke, since they will not prevent strokes due to embolization of red thrombus from the heart in atrial fibrillation, or from a deep vein (passing to the brain via a right-to-left passage, such as a patent foramen ovale). The treatment in these situations is an anticoagulant, such as heparin, warfarin, or the new direct thrombin inhibitors (*e.g.,* ximelagatran), that will make life simpler because international nor-

malized ratio testing is not necessary. (Paradoxical embolism is more common than most think. About 4% of ischemic stroke, are readily diagnosed using transcranial Doppler bubble studies, as once suspected. It should be considered when a younger person has a cryptogenic stroke, particularly if there is dyspnea or loss of consciousness at the onset, a long car or plane ride, a swollen leg, or a history of pulmonary emboli.)

If a patient taking ASA has a TIA, the right thing to do is not to double the dose, but to ask about the cause of the TIA. While awaiting the results of investigations to find the cause (Table 3), it may be reasonable to add another antiplatelet agent, or if suspicion of cardiac embolism is high, to switch to anticoagulants. CME

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Net Readings

1. Heart and Stroke Foundation of Canada: *www.heartandstroke.ca*
2. Canadian Stroke Network: *www.canadianstrokenetwork.ca*