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Prevention of Ischemic Stroke among Older Adults: Primary and Secondary

The majority of strokes occur among the older adult population. Typically, ischemic stroke can be classified by mechanism, and this is the most practical way to think about stroke since it has a direct bearing on the approach to prevention. It is not enough to simply consider that a past stroke implies a need for antiplatelet therapy or anticoagulant therapy without consideration of cause. In this article, we discuss the use of preventive strategies within the context of antithrombotics and according to stroke mechanism.

Key Words: *stroke prevention, geriatric, octogenerian, vascular risk factors, carotid stenosis, atrial fibrillation*

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Introduction

According to the Heart & Stroke Foundation of Canada, an estimated 50,000 strokes occur in Canada each year. Three hundred thousand Canadians are living with the effects of stroke, which is the fourth leading cause of death, and the second largest contributor to hospital care costs among cardiovascular diseases. The age-adjusted incidence of stroke has been declining in developed countries possibly due to efforts to lower blood pressure and reduce smoking. However, with rising rates of obesity, it is unclear if that trend will continue. Stroke risk doubles every 10 years after the age of 55 and by the age of 80, nearly one in four persons will have had a stroke.[1] Therefore, with the aging of the population, an absolute increase in the number of strokes is occurring.

Ischemic Brain Injury

The Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria categorize ischemic brain injury according to the assumed stroke mechanism. Categories include large-artery atherosclerosis, cardio-embolism, small-artery occlusion and "undetermined causes," each accounting for about 20–25% of all strokes and into the small group (approximately 10%) of "other determined causes," for example, dissection, hypercoagulable states, sickle cell disease and others.

Atrial Fibrillation

The most common cause of cardioembolic stroke is atrial fibrillation. Less data are available on atrial flutter but it is considered to be an equal risk factor for stroke. Oral anticoagulation with vitamin K antagonists (coumarols) for either persistent or paroxysmal atrial fibrillation with an INR (International Normalized Ratio) of 2.5 reduces the risk of stroke from 4.5% to 1.4% compared to placebo and is therefore recommended despite an increase of major bleeding (2.2 events per 100 patient years vs. 1.3).[2,3–9] Acetylsalicylic acid (ASA) 325 mg/day is clearly inferior to warfarin[3,8,10] but provides an alternative treatment to patients with contraindications to oral anticoagulation.[3,9] Persons under the age of 60 may be treated with ASA alone if they have lone atrial fibrillation without other risk factors.[11,12] The dilemma for physicians treating among older adults is the increased risk for intra- and extracranial bleeding.[5,13,14] Nevertheless, the use of warfarin to treat older adults with atrial fibrillation should be encouraged; with a higher baseline stroke risk, older adults have an even greater benefit from oral anticoagulation compared to the younger population.[4,15–19] There is no evidence that the routine combination of antiplatelet therapy (ASA or clopidogrel) and oral anticoagulation (warfarin) provides additional protection, however, this strategy is associated with an increased bleeding risk.[20,21] It is still uncertain when to initiate oral anticoagulation after a stroke, especially for patients with large infarcts or uncontrolled hypertension. Recommendations are to commence treatment within the first 14 days of symptom onset in minor strokes or transient ischemic attacks (TIA).[9]

Alternatives to warfarin that do not require monitoring with frequent blood tests are under development. Ximelaga-

tran, a direct thrombin inhibitor was noninferior to warfarin with fewer bleeding complications but was associated with liver toxicity and thus will not be approved.[22]

Other Cardiac Causes of Stroke

Other causes of cardioembolic stroke include mechanical prosthetic heart valves, mural thrombus after acute myocardial infarction, left ventricular thrombus associated with dilated cardiomyopathy, and rheumatic mitral valve disease. These conditions all require anticoagulation for immediate and, depending upon cause, long term management.[9,23–26] Other cardiac conditions associated with stroke include mitral valve prolapse, mitral annular calcification, and aortic valve disease, however, these should be considered minor risk factors and may be treated with antiplatelet therapy alone.[9]

The persistence of the embryonic defect in the interartrial septum—a patent foramen ovale (PFO)—is present in 20–25% of the general population and is not commonly associated with an increased risk of recurrent stroke. Among individuals under age 50 with a cryptogenic stroke, the incidence of PFO is 50%. There is no increased risk of recurrent stroke when individuals are receiving ASA. The PFO in cryptogenic stroke study (PICSS) found no additional benefit of warfarin over ASA.[27] However, in one study, if an atrial septal aneurysm is also present, the risk of recurrent stroke was 3.8% annually. This finding has not been replicated but some stroke physicians and guidelines have recommended warfarin in this situation.[28,29] In older adults, no increased risk of stroke is observed among persons with PFO. Antiplatelet therapy is required.

Transcatheter or surgical closure of PFO may only be considered in patients with recurrent cryptogenic stroke despite antithrombotic treatment since there is currently no clear evidence supporting the superiority over medical treatment.[9,29] Ongoing randomized trials like the PC-Trial (Randomized clinical trial comparing the efficacy of percutaneous closure of PFO with medical treatment in patients with cyptogenic embolism), CLOSURE 1 (Evaluation of the STARFlex® septal closure system in patients with a stroke or TIA due to the possible passage of clot of unknown origin through a PFO) and RESPECT (randomized evaluation of recurrent stroke comparing PFO closure to established current standard of care treatment) are directly comparing percutaneous PFO closure with medical therapy. It must be emphasized that at this time, the hypothesis that closure of PFO will reduce recurrent stroke remains just that, an hypothesis.

Large Artery Disease

Symptomatic Carotid Artery Stenosis

Ipsilateral carotid stenosis ≥50% account for 10% of territory ischemic strokes, 15% of TIA, and are associated with a high risk of recurrent cerebrovascular events.[30] Individuals with symptomatic high grade atherosclerotic carotid stenosis (70–99% using criteria of the North American Symptomatic Carotid Endarterectomy Trial [NASCET]) clearly benefit from carotid endarterectomy (CEA) as supported by three major prospective trials.[31–33] In cases of moderate symptomatic carotid stenosis (50–69% NASCET), CEA was less beneficial overall. Revascularization is recommended for moderate stenosis depending on patient specific factors; the best outcome is expected among male patients, older than 75 years, with recent stroke and hemispheric symptoms rather than amaurosis fugax (transient monocular visual loss). Furthermore, the patient should have at least a 5-year life expectancy, and the perioperative risk should be <6%. A key finding of re-analysis of the combined European Carotid Surgery Trial (ECST) and NASCET trial is that the benefit of surgery is most pronounced in the first 2 weeks after randomization. Persons with all degrees of stenosis and all risk categories benefited when surgery was performed early. In other words, early surgery (within 2 weeks of symptoms) is really now the standard of care.[34] The only caveat to this rule is when there is a large territory infarction; it remains unclear when to operate but it is generally recommended that the infarct be allowed to mature and heal for 4–6 weeks before surgery is undertaken (Figure 1).

Asymptomatic Carotid Artery Stenosis

In general, surgical intervention for asymptomatic carotid artery disease is not recommended. However, two large trials have shown that persons 40–75 years old with asymptomatic moderate-to-severe carotid stenosis (60–99%) and a life expectancy >5 years will benefit from CEA if the perioperative risk is <3%. Surgery is therefore offered only to a very select population[35,36] (Table 1, Figure 2) and is not proven to be beneficial on average for individuals over 75 years.

Persons undergoing CEA should receive 81–325 mg ASA/day perioperatively without discontinuation and indefinitely thereafter.[37,38] Individuals with carotid disease benefit tremendously from atorvastatin.[39] Observational evidence suggests reduced perioperative complications among patients taking statins at the time of CEA.[40,41] Caution with blood pressure management is especially important for individuals with very tight stenoses as these persons may have pressure-dependent cerebral perfusion.

In general, carotid artery stenting remains an option only for those individuals who cannot undergo surgery due to medical comorbidity. Two recent European studies have suggested that carotid stenting is inferior to endarterectomy with respect to complication rates.[42,43] Several studies are ongoing in this area. Conflicting data exist on age being a risk factor for carotid endarterectomy and stenting.[44–47]

Intracranial Stenosis

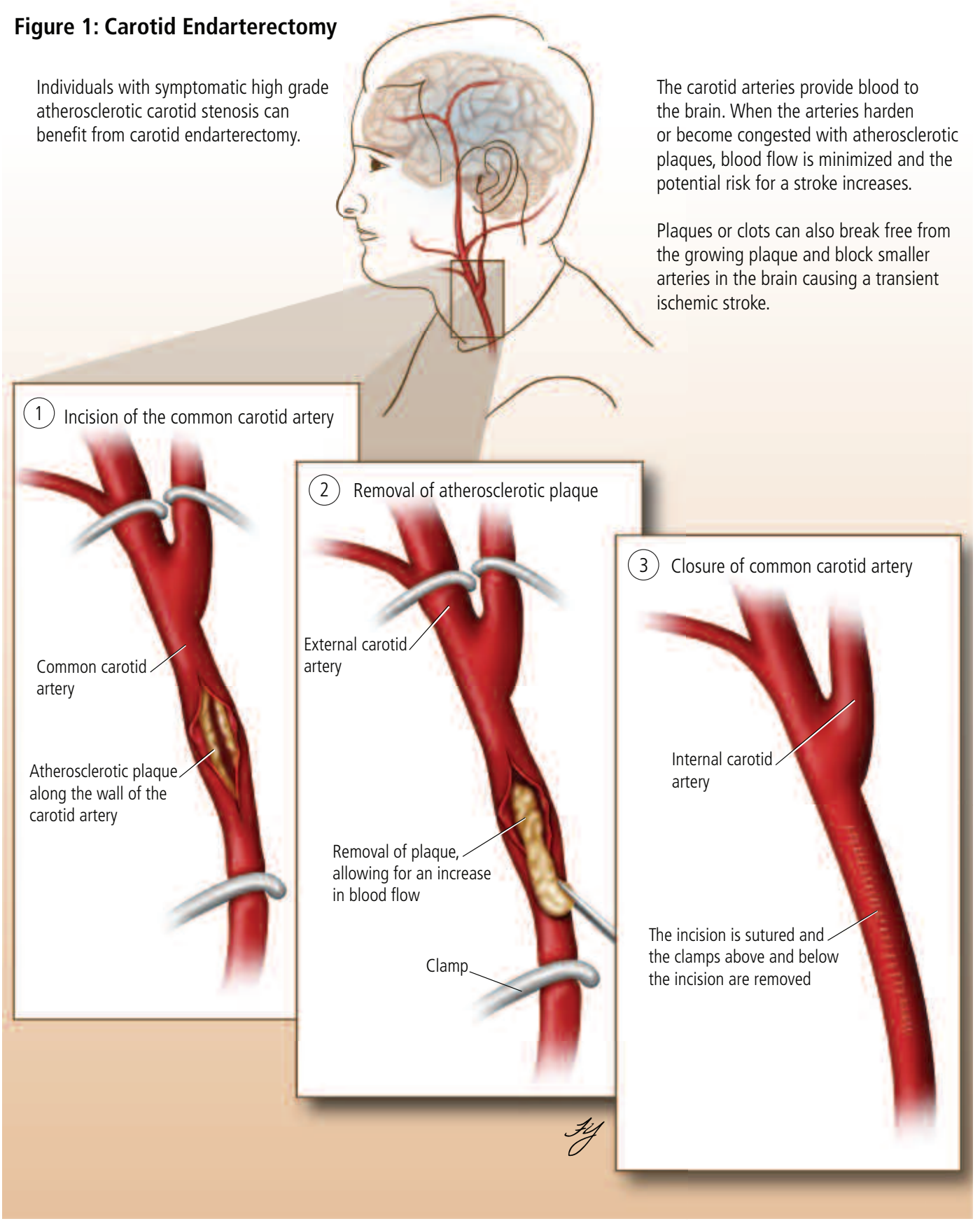
Individuals with symptomatic intracranial stenosis have a high risk of recurrent stroke. There is no significant difference in the stroke rate for carefully selected persons

Figure 1: Carotid Endarterectomy

Individuals with symptomatic high grade atherosclerotic carotid stenosis can benefit from carotid endarterectomy.

The carotid arteries provide blood to the brain. When the arteries harden or become congested with atherosclerotic plaques, blood flow is minimized and the potential risk for a stroke increases.

Plaques or clots can also break free from the growing plaque and block smaller arteries in the brain causing a transient ischemic stroke.



assigned to antiplatelet therapy and those assigned to oral anticoagulation.[48,49] Intracranial angioplasty and/or stenting has a high degree of technical success and may be considered for persons with recurrent ischemic events despite medical treatment.[9,50] However, the risk of complications is still high with a morbidity and mortality rate of up to 10%.[50–56] Long-term efficacy still needs to be evaluated. Individuals with intracranial stenosis should be evaluated by a stroke specialist.

Vertebral Artery Stenosis and Basilar Artery Stenosis

Symptomatic vertebral artery stenosis should be treated with antiplatelet therapy. Revascularization procedures are reserved for persons refractory to medical treatment.

Likewise, as with other intracranial stenosis, there is no evidence for anticoagulation therapy being superior to ASA in basilar artery stenosis. Endovascular interventional therapy is considered investigational.

Small Artery Disease—Lacunar Stroke

Management of vascular risk factors, particularly hypertension and diabetes mellitus, plays the most important role in the prevention of lacunar strokes. Warfarin does not reduce the risk of a recurrent stroke compared with antiplatelet therapy in those individuals, however, does increases the bleeding risk. The ongoing Secondary Prevention of Small Subcortical Strokes (SPS3) trial, which focuses exclusively on lacunar stroke, will provide much needed new information on preventing lacunar stroke.

Other Specific Causes

Dissection

The risk of a recurrent stroke after carotid or vertebral artery dissection is low and spontaneous healing with recanalization occurs in many patients. Although anticoagulant therapy is often initiated, meta-analyses did not find any significant difference in stroke prevention compared to antiplatelet agents.[57] Eligibility for stent placement or surgical therapy in persons with recurrent stroke despite adequate medical treatment should be assessed by a stroke specialist. In general, dissection is rare in the older adult population and most dissection patients can be managed with antiplatelet therapy alone.

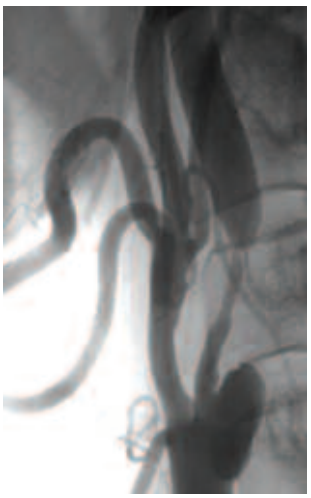


Figure 2: Long segment of irregular narrowing of left distal common and proximal internal carotid artery, greatest stenosis measures about 80% using NASCET criteria. Figure courtesy of Department of Medical Imaging, Division of Neuroradiology, Foothills Medical Centre, University of Calgary.

Hyperhomocysteinemia

Hyperhomocysteinemia doubles the stroke risk. One meta-analysis has concluded that vitamin supplementation modestly reduces stroke risk.[58] The ongoing Vitamins to Prevent Stroke (VITATOPS) trial, which has nearly completed recruitment of 8,000 persons, will allow for a definitive statement on the use of vitamins in stroke prevention.

Inherited Thrombophilias or Acquired Hypercoagulable States

Inherited thrombophilias or acquired hypercoagulable states are not clearly associated with an increased risk of arterial ischemic stroke, especially among older adults. Nevertheless, persons who have had stroke(s) with either condition should be worked up for deep venous thrombosis and decisions about antithrombotic treatment should be made based upon findings. A retrospective multicentre review of individuals with sickle cell disease (SCD) and stroke suggested treatment other than antiplatelet agents and control of vascular risk fac-

Table 1: Recommendations for Carotid Endarterectomy Depending on Grade of Stenosis using NASCET Criteria.

Stenosis	Recommendation
Symptomatic patients	
High grade (70–99%)	Carotid endarterectomy
Moderate (50–69%)	Carotid endarterectomy if patient's life expectancy > 5years and perioperative stroke/death rate <6%
Mild (<50%)	Medical treatment alone
Asymptomatic patients	
60–99%	Carotid endarterectomy may be considered if patient 40–75years old, life expectancy >5years, perioperative stroke/death rate <3%
<60%	Medical treatment alone

Source: adapted from recommendations of the American Academy of Neurology.[97]

tors. Suggested treatment includes regular blood transfusions sufficient to suppress native hemoglobin S formation.[59] Long-term transfusion complications must be considered. Expert consultation, especially for alternative treatment options, such as hydroxyurea and bypass surgery in cases of advanced occlusive disease (e.g., Moya-Moya), is advised.

Antiphospholipid Antibody Syndrome

Data investigating the association between antiphospholipid antibody (APL) prevalence and stroke recurrence, especially among older adults, is controversial.[60,61] Antiplatelet therapy is considered to be sufficient in cases of cryptogenic stroke and APL antibodies. Notice should be made that a test of two positive anticardiolipid antibodies needs to be confirmed, ideally after a time of 3 months. Persons who have had a stroke and who meet the criteria for APL syndrome with venous and arterial occlusive disease in multiple organs should receive oral anticoagulation with a target INR of 2.5.

Treatment of Vascular Risk Factors

In many instances (25% of cases), a specific stroke mechanism cannot be determined and a general approach to prevention must be taken. In this situation, addressing both stroke risk states (e.g., atrial fibrillation) and stroke risk factors is the only approach to prevention. The most important risk factor for stroke is hypertension. This is true for both primary and secondary stroke prevention and indeed, the primary benefit of treating hypertension is the prevention of neurological disease (stroke and vascular dementia).

Hypertension

A reduction of systolic blood pressure by 5–6 mmHg and/or of diastolic blood pressure by 2–3 mmHg leads to approximately 40% relative and 0.5% absolute risk reduction of stroke.[62] The positive effect is seen in all age groups and in isolated systolic hypertension.[63] Preventive efficacy increases with the extent of blood pressure lowering in a linear fashion.[64–66] The minimal goal blood pressure (BP) for individuals with hypertension is <140/90 mmHg or <130/80 mmHg for those with diabetes mellitus or chronic kidney disease.[67] Current trials are evaluating whether lower targets result in even greater risk reduction. Indeed, the risk of stroke starts to measurably increase as the systolic pressure rises above 115 mmHg.[65]

Lifestyle modifications, including weight reduction in obese or overweight individuals,[68,69] consumption of a sodium-reduced combination diet (rich in fruits, vegetables, low-fat dairy foods and potassium, containing smaller amounts of red meat, sugar, sweets, total/ saturated fat and cholesterol),[70,71] regular physical activity,[72,73] and alcohol reduction,[74] are as important as medical treatment for BP management. Lifestyle measures may be equivalent to one additional blood pressure medication.

The optimal drug regimen remains uncertain; all major classes of drugs (angiotensin-converting enzyme inhibitors [ACEI], angiotensin receptor blockers [ARB], beta-blockers, calcium antagonists, and diuretics) may be initiated.[75–77] Some data support the preferential use of diuretics or the combination of diuretics and ACEIs.[17,78] Angiotensin receptor blockers seem to have a positive effect on vascular events and mortality beyond the BP lowering effect.[79] The alpha blocker doxazosin was associated with a higher risk of congestive heart failure compared to chlorthalidone and therefore alpha blockers are not recommended at first line treatment.[80] In general, the target BP, rather than the means of obtaining it, is the critical issue.

In the setting of an acute ischemic stroke (within the first week of onset), the optimal time to start antihypertensive medication is uncertain and a cautious approach to BP management is recommended.[81] Ongoing trials are addressing this area.

Diabetes Mellitus

Diabetes mellitus (DM), a clear risk factor for stroke, is diagnosed with repeated fasting plasma glucose levels >7.0 mmol/l or casual >11.1 mmol/l. Glucose control by diet, oral hypoglycemic drugs, and insulin reduces vascular events and is recommended to normoglycemic levels (≤5.6 mmol/l) for primary and secondary prevention of stroke. A Hemoglobin A1c level ≤7% reflects adequate control. Rigorous BP control with a target of ≤130/80 mmHg in individuals with DM, both type I and II, significantly reduces the incidence of stroke.[82,83] All major classes of antihypertensive drugs are appropriate for BP management. Nevertheless the American Diabetes Association recommends a regimen including either ACE inhibitors or angiotensin converting enzyme blockers since those have favourable effects on the progression of diabetic nephropathy.[84] Independent of baseline LDL cholesterol (LDL-C), statin use among persons with diabetes reduces both cardio- and cerebrovascular events.[85] An LDL-C target of 1.8 mmol/l is recommended.

Cholesterol

Several trials demonstrated that lipid-lowering statins reduce the risk of stroke among persons with coronary heart disease (CHD).[86, 87] The recent Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study showed clear benefit of a fixed dose of 80 mg atorvastatin for individuals with recent stroke and without a history of CHD. Not surprisingly, the trial was driven by stroke reduction in persons with carotid artery stenosis. However, a small increase in the incidence of hemorrhagic stroke was observed.[88] Target LDL-C levels depend on the individual risk profile. The goal for high-risk patients (established CHD plus multiple vascular risk factors) is ≤1.8 mmol/l.9 Individuals without major risk factors except CHD should aim for an LDL-C level of £2.6 mmol/l. Aside from medical treatment, the management of dyslipidemia must include dietary changes, weight reduction and an increase in physical activity.

Smoking

Smoking, active and passive, is a major independent risk factor for ischemic stroke.[89,90] Compared with nonsmokers, the risk for a cerebrovascular event is up to twice as high[91] among smokers and normalizes 5 years after cessation. Smokers should therefore be strongly advised to quit and pharmacotherapeutical or psychological support provided where necessary.

Alcohol

Light alcohol consumption (up to two drinks, or 24 g, or 1.0 oz alcohol per day) was seen to be protective rather than an increase in the risk of stroke. On the other hand, heavy alcohol consumption (>5 drinks per day) is associated with a markedly higher risk for cerebrovascular events when compared to nondrinkers.[92] Elimination or reduction to ≤2 drinks of alcohol per day is recommended.

Obesity

Obesity contributes to the major risk factors for stroke: hypertension, diabetes and dyslipidemia. Also, a significant independent association between abdominal obesity and stroke was found.[93] Weight loss or maintaining a healthy weight (body mass index 18.5–24.9 kg/m2) are very important. Management includes a healthy diet rich in fruits and vegetables, physical activity, and, where applicable, behavioural counselling.

Physical activity has beneficial effects on the above-mentioned risk factors, on blood rheology, and platelet reactivity, and leads to a gender-independent risk reduction of stroke. Activities that are vigorous enough to work up a sweat or increased heart rate are required for these beneficial effects.[94–96] For persons disabled after stroke, it is essential to exercise and regain prestroke levels of activity where possible; professional supervised physiotherapy is strongly recommended.

Conclusion

The approach to stroke prevention depends upon mechanism. It is important to critically assess the causes of stroke in order to develop a rational stroke prevention approach. While treating vascular risk factors is important for all stroke patients, and remains the only option when stroke or TIA has an undefined mechanism, simply changing antiplatelet therapies is no longer an acceptable approach to stroke care.

No competing financial interests declared.

Key Points

Three hundred thousand Canadians are living with the effects of stroke; it is the fourth leading cause of death, and the second largest contributor to hospital care costs among cardiovascular diseases.

Typically, ischemic stroke can be classified by mechanism, and this is the most practical way to think about stroke since it has a direct bearing on the approach to prevention.

In many instances (25% of cases), the stroke mechanism cannot be determined and a general approach to prevention must be taken.

Management of vascular risk factors, particularly hypertension and diabetes mellitus, plays the most important role in the prevention of lacunar strokes.

While treating vascular risk factors is important for all stroke patients, and remains the only option when stroke or TIA has an undefined mechanism, simply changing antiplatelet therapies is no longer an acceptable approach to stroke care.

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