STROKE: SECONDARY PREVENTION

OBJECTIVE:
To provide an evidence-based approach to the secondary prevention of ischemic stroke or transient ischemic attack (TIA).

BACKGROUND:
Secondary prevention refers to approaches to reduce the risk of recurrent vascular events in patients who have already suffered a stroke or TIA. This guide focuses on the risk factors most relevant to stroke recurrence, and includes:

1. Lifestyle risk factor modification
2. Smoking cessation
3. Blood pressure management
4. Antithrombotic therapy
5. Lipid management
6. Diabetes management
7. Sleep apnea
8. Management of carotid stenosis
9. Anticoagulation for atrial fibrillation
10. Management of patent foramen ovale (PFO)

1. LIFESTYLE RISK FACTOR MODIFICATION
(See also Canadian Stroke Best Practices @ http://www.strokebestpractices.ca/)

- All patients with prior stroke or TIA should be evaluated for all modifiable risk factors and should be given appropriate counselling and information to support positive changes in lifestyle and reduction in modifiable risk factors.
- Balanced diet - Promote a diet high in fresh fruits, vegetables, low-fat dairy products, soluble fibre, whole grains, protein from plant sources, and low in saturated fat, cholesterol (<200 mg daily for patients at increased vascular risk) and sodium. Evidence suggests that the Mediterranean diet reduces the occurrence of stroke.
- Sodium intake – Avoiding excessive salt intake (daily sodium intake from all sources should be <2,000 mg daily) may be beneficial. Patients should be made aware that most salt intake comes from consuming processed foods; therefore, excess salt intake can be reduced by restricting consumption of processed foods.
- Exercise - Encourage moderate exercise, if possible, including brisk walking, jogging, cycling, or swimming 4-7 days per week in addition to routine activities of daily living. The exercise target should be at least 150 minutes of moderate to vigorous activity per week, in episodes of 10 minutes or more.
• **Weight** - Target a BMI of 18.5 to 25 kg/m² or a waist circumference of <102 cm for men and <88 cm for women.

• **Alcohol** - Limit to 10 drinks per week, 2 drinks per day, or 3 drinks on any single occasion for women, and 15 drinks per week, 3 drinks per day or 4 on any single occasion for men (excluding pregnant women where any alcohol intake is not recommended).

2. **SMOKING CESSATION**

(See also Canadian Stroke Best Practices @ http://www.strokebestpractices.ca/)

• Address smoking cessation and a smoke-free environment at every healthcare encounter for active smokers.

• There is a lack of evidence regarding the timing to initiate nicotine replacement therapy in patients following a stroke. Expert opinion suggests this may begin as soon as it is medically appropriate and should take into consideration the stroke type and severity, patient interest, and physician comfort level.

• In general, nicotine replacement therapy is safer than continuing to smoke.

• Three classes of pharmacological agents considered to be first-line agents for smoking cessation are: nicotine replacement therapy, varenicline and bupropion.

3. **BLOOD PRESSURE MANAGEMENT**

(See also Canadian Stroke Best Practices @ http://www.strokebestpractices.ca/ and Hypertension Canada @ http://guidelines.hypertension.ca/)

a) Hypertension monitoring:

• **Hypertension is the single most important modifiable risk factor for stroke.**

• Ideally, all patients should have their BP measured at each healthcare encounter and no less than once annually.

• Standardized measurement techniques should be used as outlined by the Hypertension Canada guidelines. These can be reviewed at: http://guidelines.hypertension.ca/diagnosis-assessment/measuring-blood-pressure/.

b) Hypertension management:

• For patients who have already had a stroke or TIA (including those with nondiabetic chronic kidney disease), BP lowering treatment is recommended to consistently achieve lower than 140/90 mm Hg.

• For patients with stroke/TIA and diabetes, a BP target lower than 130/80 mm Hg is recommended and in patients who have had a lacunar stroke, the systolic BP should also be less than 130 mm Hg.

• Refer to Hypertension Canada for specifics on antihypertensive therapy for patients with cerebrovascular disease (http://guidelines.hypertension.ca/prevention-treatment/hypertension-with-stroke/).

• Randomized trials have not defined the optimal time to initiate BP lowering therapy after stroke or TIA, but it should be initiated or modified before discharge from hospital.
4. ANTITHROMBOTIC THERAPY

(See also Canadian Stroke Best Practices @ http://www.strokebestpractices.ca/)

- This guide assumes that a search for atrial fibrillation (AF) has been conducted, especially in patients with a presumed embolic ischemic stroke that is of uncertain source, since this will warrant anticoagulant therapy if found.
- All patients with ischemic stroke or TIA should be prescribed antiplatelet therapy for secondary prevention of recurrent stroke unless there is an indication for anticoagulation.
- Acetylsalicylic acid (ASA; 81 mg), ASA (25 mg) combined with extended-release dipyridamole (200 mg), or clopidogrel (75 mg) are all appropriate choices for long-term secondary prevention.
- Short-term concurrent use of ASA 81 mg and clopidogrel 75 mg for up to 30 days following minor stroke or TIA in the acute (<24 hours) setting is recommended; however, combination therapy for a longer period is associated with increased risk of hemorrhagic complications and is not recommended for secondary stroke prevention, unless there is an alternate indication (e.g. recent acute coronary syndrome).
- In the COMPASS trial, which compared rivaroxaban 5 mg bid, rivaroxaban 2.5 mg bid + ASA and ASA alone in high risk patients with coronary artery disease (CAD), peripheral artery disease (PAD) or both; the overall risk of stroke was decreased during a mean follow-up of 23 months from 1.6% with ASA alone to 0.9% with rivaroxaban + ASA (relative risk reduction 42%; p<0.001). The strongest predictor of stroke during follow-up was a prior stroke history, which was reported in 4% of participants (those with stroke in last month, hemorrhagic stroke or lacunar stroke were excluded). In this subgroup, the absolute stroke reduction was 2.3% per year with rivaroxaban + ASA versus ASA alone; suggesting a role for this regimen in secondary stroke prevention in those with CAD, who would meet Health Canada indications.
- There is currently a lack of evidence to guide management if a patient has a TIA or stroke while already on an antiplatelet agent. Compliance with the antiplatelet agent should be assessed. Some clinicians switch to an alternate antiplatelet agent or use dual antiplatelet (aspirin and clopidogrel) therapy for a short interval (see above). Careful consideration should be given to stroke mechanism and the patient should be re-investigated for stroke/TIA etiology to ensure appropriate antithrombotic medication (e.g. oral anticoagulant rather than antiplatelet if stroke mechanism is cardioembolic or carotid endarterectomy/stent if significant carotid stenosis).

5. LIPID MANAGEMENT

(See also Canadian Stroke Best Practices @ http://www.strokebestpractices.ca/)

- Patients who have had an ischemic stroke or TIA should have their serum lipid levels assessed and aggressively managed if elevated.
- A statin drug should be prescribed as secondary prevention to achieve an LDL cholesterol under 2.0 mmol/L (or a non-HDL-C <2.6 mmol/L) or >50% reduction in LDL cholesterol from baseline. For individuals with stroke and acute coronary syndrome (and established coronary
disease), treatment to more aggressive targets (LDL-C <1.8 mmol/L or >50% reduction) should be considered.

- Ezetimibe is recommended as second line therapy for those unable to achieve target LDL cholesterol levels on maximally tolerated statin therapy.
- Bile acid sequestrants or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors should be considered for those not at target despite maximally tolerated statin +/- ezetimibe therapy.
- Statin therapy is not indicated for prevention of intracerebral hemorrhage.
- **REDUCE-IT** examined the use of icosapent ethyl versus placebo in patients with CV disease or with diabetes and additional risk factors who had been receiving statin therapy and had fasting triglyceride levels between 1.69-5.63 mmol/l on a stable dose of statin. A total of 11.5% of study participants had previous stroke or TIA. During a median duration of follow-up of 4.9 years, the overall risk of stroke (fatal or non-fatal) was decreased from 3.3% with placebo to 2.4% in those randomized to icosapent ethyl (relative risk reduction of 28%, p=0.01). Health Canada has approved icosapent ethyl to reduce the risk of cardiovascular events (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularization or hospitalization for unstable angina) in statin-treated patients with elevated triglycerides, who are at high risk of cardiovascular events due to established cardiovascular disease or diabetes, and at least one other cardiovascular risk factor.

6. **DIABETES MANAGEMENT**

- For diabetic patients with an ischemic stroke or TIA, HbA1C should be measured.
- Most patients with diabetes and prior stroke or TIA should be treated to achieve a HbA1C level ≤ 7.0%.
- Diabetes Canada Guidelines should be referred to regarding the addition of sodium glucose-linked transporter 2 (SGLT2) inhibitors and glucagon like peptide 1 (GLP1) agonists (e.g. empagliflozin, canagliflozin and liraglutide) to metformin in patients with stroke/TIA and diabetes not at glycemic targets ([http://guidelines.diabetes.ca/cpg/chapter23](http://guidelines.diabetes.ca/cpg/chapter23)).
- The **SUSTAIN-6** trial reported a reduction in major cardiovascular events over 104 weeks in patients with type 2 diabetes and high cardiovascular risk from 8.9% in the placebo group to 6.6% in those randomized to the once weekly GLP1 agonist, semaglutide (relative risk reduction 26%, p<0.001 for noninferiority). Nonfatal stroke occurred in 2.7% and 1.6%, respectively (relative risk reduction of 39%, p=0.04). Of study participants, 10.5% had previous stroke. Although a post-hoc analysis reported a there was a similar trend favoring the intervention in those with prior myocardial infarction or stroke, the reduction in events was not statistically significant.

7. **SLEEP APNEA**

- Obstructive sleep apnea (OSA) is a risk factor for stroke and is also present in many patients following a stroke. However, based on the results of the recent SAVE trial, there are no longer recommendations for universal sleep apnea screening and treatment in patients post...
stroke/TIA. Screening and treatment for sleep apnea should be based on symptoms, regardless of previous stroke status.

8. **MANAGEMENT OF CAROTID STENOSIS**

(See also Canadian Stroke Best Practices @ [http://www.strokebestpractices.ca/](http://www.strokebestpractices.ca/))

- Patients with TIA or non-disabling stroke who have symptomatic ipsilateral 50-99% internal carotid artery stenosis (measured by non-invasive imaging modalities) should be evaluated by a neurosurgeon/vascular surgeon with stroke expertise as soon as possible. Carotid stenosis should ideally be measured by CT angiogram (CTA) to guide surgical decision-making.
- Selected patients (especially those with mild stroke or TIA) should be offered carotid endarterectomy as soon as possible, with the goal of operating within 14 days of the onset of symptoms once the patient is clinically stable. Carotid stenting should be considered in the above patient group if they are not a candidate for carotid endarterectomy due to technical, anatomic or medical reasons (e.g. high cardiac risk).
- Patients with TIA or non-disabling stroke and symptomatic ipsilateral internal carotid artery stenosis <50% should be medically managed with vascular risk modification including antiplatelet and statin therapy, BP lowering, diabetes control, and smoking cessation.

9. **ANTICOAGULATION FOR ATRIAL FIBRILLATION**

- The Clinical Guide: [Stroke Prevention in Atrial Fibrillation](http://www.strokebestpractices.ca/) can provide additional details.
- In embolic stroke of uncertain source, atrial fibrillation is relatively common; therefore, in these patients, a thorough cardiac evaluation should be done to rule out underlying atrial fibrillation (e.g. 48-hour Holter monitor, loop recorder). In older (≥ 55 years) patients with embolic stroke of uncertain source who do not have atrial fibrillation on one short term electrocardiographic monitoring (24- to 48-hour Holter), prolonged cardiac monitoring for at least 2 weeks and up to 4 weeks is recommended.
- At present there is no evidence to support empiric use of anticoagulation in patients with embolic stroke of uncertain source.
- There are few indications for combination antiplatelet and anticoagulation therapy, so monotherapy with anticoagulation is suggested unless there is a specific medical indication for both, as the risk of bleeding is increased.

10. **MANAGEMENT OF PATENT FORAMEN OVALE (PFO)**

(See also Canadian Stroke Best Practices @ [http://www.strokebestpractices.ca/](http://www.strokebestpractices.ca/))

- Patients with a cerebral ischemic event attributed to a PFO should have an evaluation by physicians with cerebrovascular and cardiovascular expertise.
- PFO device closure and antiplatelet therapy is favored for patients 18 to 60 years of age with a nonlacunar embolic-appearing ischemic stroke or transient ischemic attack with positive neuroimaging or cortical symptoms with no other evident cause despite a comprehensive evaluation. Patients with a large right-to-left interatrial shunt and/or an associated atrial septal aneurysm (characteristics that suggest an increased risk for paradoxical embolism)
appear most likely to benefit from this intervention. New-onset atrial fibrillation is a potential adverse effect of PFO device closure.

- The benefit of PFO closure for patients requiring long-term anticoagulation for another indication is uncertain.

**OTHER RELEVANT THROMBOSIS CANADA CLINICAL GUIDES:**

- Acetylsalicylic Acid (ASA)
- Clopidogrel (Plavix®)
- Rivaroxaban (Xarelto®)
- Stroke Prevention in Atrial Fibrillation

**REFERENCES:**


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Please note that the information contained herein is not to be interpreted as an alternative to medical advice from your doctor or other professional healthcare provider. If you have any specific questions about any medical matter, you should consult your doctor or other professional healthcare providers, and as such you should never delay seeking medical advice, disregard medical advice or discontinue medical treatment because of the information contained herein.