Ischemic Stroke or TIA: Secondary Prevention

Thrombosis Canada
Thrombose Canada

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. Secondary prevention of ischemic stroke and TIA involves control of modifiable risk factors, antithrombotic therapy, and aetiology-specific interventions. Individualized education, counselling and therapeutic interventions aligned to the patient's values and preferences together with shared decision-making optimize engagement and long-term adherence to secondary prevention.

This guide is largely aligned with the Canadian Stroke Best Practices – Recommendations: Secondary Prevention of Stroke (http://www.strokebestpractices.ca/recommendations/secondary-prevention-of-stroke)

Control of Modifiable Risk Factors:

All modifiable risk factors should be evaluated and addressed in all patients with prior stroke or TIA. Involving allied healthcare services where indicated may help control risk factors (e.g., nutrition, kinesiology, smoking cessation programmes, psychosocial support groups).

1. Positive lifestyle changes

Healthy balanced diet:

- Promote a healthy diet, which comprises plenty of fresh fruits and vegetables, whole grain foods, proteins from plant sources (e.g., nuts, legumes), low-fat milk and diary products, and other low-fat sources of proteins (e.g., fish, lean meat, poultry). Recommend reducing saturated fat, cholesterol (<200 mg daily for patients at increased vascular risk) added sugars and sodium, and processed food. Evidence suggests that the Mediterranean-type or DASH (Dietary Approach to Stop Hypertension) diet reduces the occurrence of stroke. Refer patients to Canada's Food Guide (https://food-guide.canada.ca).

Sodium intake:

- Target a sodium intake from all sources of <2,000mg daily. Inform patients that most salt intake comes from consuming processed foods.

Physical activity:

- Encourage medical activity in medically stable patients. Target ≥10-minute episodes of aerobic exercise over 4-7 days per week, totalizing ≥150 minutes in addition to routine activities of daily living. Fitness assessment and the involvement of healthcare professionals (e.g., kinesiologist, physiotherapist) may help determine the type of exercise and appropriate intensity, considering functional limitations and co-morbidities.

Weight:

- Target a BMI of 18.5 to 24.9 kg/m^2 or a waist circumference of <102 cm for men and <88 cm for women. Other targets may apply to non-Caucasian patients.

Alcohol:

- Canadian recommendations have changed over the years. These can be reviewed at: https://www.ccsa.ca/canadas-guidance-alcohol-and-health. The main principle is: "Drinking less is better". Tips to drink less are provided in an infographic summary.
- Inform patients of the risks associated with alcohol consumption and support them in making decisions.
- No amount or kind of alcohol is good for health. Even a small amount of alcohol can be damaging to health, regardless of age, sex, gender, ethnicity, tolerance for alcohol, or lifestyle.
- Cancer risk increases at ≥3 drinks/week, and stroke and heart disease risk at ≥7/week.

Smoking cessation:

- Address smoking cessation and a smoke-free environment at every healthcare encounter for active smokers. Three classes of pharmacological agents considered to be first-line agents for smoking cessation are: nicotine replacement therapy, varenicline and bupropion.
- 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.
- E-cigarettes may help quit smoking. However, the evidence around their population-based effectiveness is not clear. Furthermore, vaping may increase blood pressure. In addition, some smokers continue to vape even after quitting cigarettes, contrasting with nicotine replacement therapy. Most commonly individuals engage in both and a vascular risk modification strategy should target cessation of both modalities.

Oral contraceptives and hormone replacement therapy:

- Advise most women of reproductive age who are at risk of recurrent ischemic stroke to avoid systemic estrogen-containing contraceptives. Management alternatives include progesterone-only oral contraceptives, progesterone-only or non-hormonal intra-uterine devices, and barrier contraception. Following menopause, avoid hormone replacement therapy, which is associated with thrombosis.

2. Hypertension

Monitor blood pressure (BP):

- 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/.

Treat hypertension to established therapeutic targets:

- The ACE inhibitor and thiazide/thiazide-like diuretic combination is recommended following ischemic stroke or TIA. The ACE inhibitor and ARB combination is not recommended.
- Randomized trials have not defined the optimal time to initiate BP lowering therapy following stroke or TIA, but it should be initiated or modified after the acute phase and before discharge from hospital.
- BP should be consistently <140/90 mm Hg in most patients (including those with nondiabetic chronic kidney disease), <130/80 mm Hg in diabetic patients. Furthermore, in patients with small subcortical strokes (lacunar strokes), systolic BP <130 mm Hg is reasonable. A similar target is reasonable for maintenance in patients with a history of intracerebral hemorrhage.
- Higher BP targets might be considered to avoid hemodynamic stroke in patients with recent neurological deficits secondary to critical intracranial or extracranial arterial stenosis, but the previous BP targets hold in the long term.

3. Dyslipidemia

Monitor dyslipidemia:

- Measure serum lipid levels (triglycerides, LDL-cholesterol, HDL-cholesterol, non-HDL-cholesterol, total-cholesterol). Non-fasting testing is generally recommended. Fasting testing is used for patients with triglycerides >4.5 mmol/L.

Treat dyslipidemia to therapeutic targets:

- Treat aggressively, especially in patients with evidence of atherosclerosis or small artery disease (lacunar stroke).

- Promote positive lifestyle changes, including lipid-lowering dietary changes and physical activity, to improve the lipid profile.
- Use statin drugs to achieve an LDL-cholesterol level ≤1.8 mmol/L.
- Consider treatment intensification in patients receiving maximally tolerated statin dose, including ezetimibe or PCSK9 inhibitors or both if LDL remains >1.8 mmol/L, and icosapen ethyl 2 g BID if triglycerides are ≥1.5 mmol/L in patients with cardiovascular disease or with diabetes plus additional vascular risk factors.
- For more details refer to the Canadian Cardiovascular Society Guidelines 2021 (https://doi.org/10.1016/j.cjca.2021.03.016).

4. Diabetes

Monitor diabetes:

- Screen for diabetes with either a fasting plasma glucose, or 2-hour postprandial plasma glucose, or glycated hemoglobin (A1C), or 75 g oral glucose tolerance test.
- Measure A1C in diabetic patients with stroke as part of their comprehensive assessment.

Treat diabetes to established therapeutic targets:

- Most patients with diabetes and prior stroke or TIA should be treated to achieve a A1C level ≤ 7.0%. Most patients achieve this A1C target if preprandial or fasting blood glucose levels are at 4.0-7.0 mmol/L or if postprandial levels are at 5.0-10.0 mmol/L.
- Sodium glucose-linked transporter 2 (SGLT-2) inhibitors (e.g., empagliflozin, canagliflozin) and glucagon-like peptide 1 (GLP1) receptor agonists (e.g., liraglutide, semaglutide) should be considered in type 2 diabetic patients not at glycemic targets despite standard oral antihyperglycemic agents (metformin).
- Refer to Diabetes Canada Guidelines for further information (http://guidelines.diabetes.ca/cpg/chapter23).
- In non-diabetic patients treated with pioglitazone for insulin resistance, the reduction of cardiovascular events is offset by increased risks of bone fracture and bladder cancer.

Antithrombotic Therapy

1. Antiplatelet treatment

Acute ischemic stroke or TIA:

- Antiplatelet treatment should be initiated as soon as possible following ischemic stroke or TIA, once intracerebral hemorrhage has been excluded by brain imaging. Following ischemic stroke or TIA, brain imaging should be obtained as soon as possible to exclude intracerebral bleeding, and to initiate antiplatelet treatment without delay.
- In ischemic stroke patients treated by intravenous thrombolysis, antiplatelet therapy should be initiated only after exclusion of a hemorrhagic transformation on repeat brain imaging done 24 hours after thrombolysis. In select cases, earlier treatment may be indicated – expert consultation with a stroke neurologist is recommended.

- Ischemic stroke patients not already on antiplatelet agents should rapidly receive a loading dose of acetylsalicylic acid (ASA) of 160 mg, followed by 80 mg daily. Patients with ischemic stroke or TIA despite antiplatelet therapy should be assessed for treatment compliance and may be treated with the same agent or switched to another.
- In patients with acute nondisabling minor ischemic stroke, not treated with tPA/TNK (NIHSS <4) or TIA of noncardioembolic etiology, who are not at high risk of bleeding, the combination of clopidogrel (300 or 600 mg loading dose followed by 75 mg daily) and ASA (160 mg loading dose followed by 80 mg daily) is recommended for the first 21 days post-event, followed by antiplatelet monotherapy (ideally started as soon as possible after the event, however recent data suggests benefit even if initiated up to 72 hrs). The combination of ticagrelor (180 mg loading dose followed by 90 mg daily) and ASA is another reasonable option for the first 30 days post-event.
- Dysphagia screening should precede oral administration of medications for all acute stroke patients. For patients with dysphagia, oral antiplatelet agents should be avoided. ASA can be administered by enteral tube (80 mg daily) or rectal suppository (325 mg daily). Clopidogrel may be administered by enteral tube (75 mg daily).

Long-term prophylaxis following ischemic stroke or TIA:

- Antiplatelet therapy is recommended, unless an anticoagulant treatment is indicated.
- Antiplatelet treatment options include ASA 80 mg daily, clopidogrel 75 mg daily, and combined ASA-dipyridamole extended-release 25/200 mg BID.
- For patients with stroke or TIA due to a symptomatic 70-99% intracranial stenosis, and low bleeding risk, the combination of ASA and clopidogrel should be considered for the first 3 months post-ischemic stroke or TIA, followed by indefinite treatment with a single antiplatelet agent.
- In patients with coronary artery disease or peripheral vascular disease (including asymptomatic carotid artery stenosis of 50% or more), low bleeding risk, no cardioembolic source for the index stroke and no history of lacunar or hemorrhagic stroke, rivaroxaban 2.5 mg bid may be combined to ASA 80 mg daily after the first month post-ischemic stroke or TIA.

2. Anticoagulation for atrial fibrillation

Patients with ischemic stroke or TIA due to atrial fibrillation:

- The **Clinical Guide:** **Stroke Prevention in Atrial Fibrillation** can provide additional details.
- ASA is used in the acute phase of ischemic stroke (see above).
- Following the acute phase of ischemic stroke, oral anticoagulant therapy is strongly recommended, over single or dual antiplatelet therapy. Unless medically indicated otherwise (e.g., <1 year post-PCI), antiplatelet therapy is discontinued after the acute phase of stroke, once full-dose anticoagulation is achieved. Bridging with heparin is not recommended.
- The optimal time to switch from ASA to oral anticoagulant treatment after the acute phase of stroke is undetermined. In general, full-dose anticoagulation is considered to be safe 3 days post-event for minor strokes and smaller brain infarcts, 6-7 days post-event for moderate severity strokes and moderate-sized infarcts, and 12-14 days post-event for severe strokes and larger infarcts, however recent data suggests that earlier initiation of anticoagulation (after 48 hrs in mild to moderate strokes and >6-7 days in cases of large/severe strokes) may be safe – and timing of initiation of anticoagulation therapy should be individualised. Repeat brain

imaging is recommended <24 hours before initiating anticoagulant therapy to exclude the presence of hemorrhagic transformation of the brain infarct.
    - For patients experiencing TIA (no residual neurological symptoms and no acute infarct and hemorrhage on neuroimaging), anticoagulation may be started in the first 24 hours post-event (no ASA-bridging).
    - In atrial fibrillation patients experiencing ischemic stroke or TIA despite anticoagulant treatment, assess for and address other stroke aetiologies, anticoagulant nonadherence and underdosing, drug-drug interactions, and uncontrolled vascular risk factors. Adding ASA to anticoagulant treatment specifically for stroke prevention is not recommended because of increased bleeding risk without potential benefit.

Patients with embolic stroke of uncertain source (ESUS):

- Atrial fibrillation can be present in a subgroup of ESUS patients; therefore, a thorough cardiac evaluation should be done to rule out underlying atrial fibrillation. In older (≥ 55 years) ESUS patients 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 is recommended.
- At present there is no evidence to support empiric use of anticoagulation in ESUS patients.

Aetiology-specific Interventions

1.Ischemic stroke or TIA secondary to atherosclerosis

- Patients with TIA or non-disabling stroke attributed to an ipsilateral 50-99% internal carotid artery (ICA) stenosis should be evaluated without delay by a health professional with stroke expertise to determine whether carotid revascularization is indicated.
- CT-angiography or contrast-enhanced MR-angiography is recommended to confirm the degree of ICA stenosis and guide surgical decisions based on the vascular anatomy from the aortic arch to the intracranial arteries. Carotid ultrasound may be required if the degree of stenosis cannot be reliably established from CT- or MR-angiography.
- In men with symptomatic 50-99% ICA stenosis and women with symptomatic 70-99% ICA stenosis, carotid revascularization (by endarterectomy or stenting) should be performed as soon as possible (ideally <14 days post-event). Women with symptomatic 50-69% ICA stenosis and a high risk of recurrent events may also benefit from revascularization. The choice between endarterectomy or stenting requires expert consultation with the appropriate surgical service.
- It may be reasonable to delay carotid intervention by 48 hours for moderate/ severe stroke to attenuate the perioperative risks. Index stroke severity and perioperative risks should always be balanced with the risk of early stroke recurrence.
- The benefit of carotid revascularization is uncertain in patients with symptomatic 50-99% stenosis who survived a moderate to severe stroke.
- For patients with symptomatic vertebral artery or intracranial artery stenosis, medical therapy is recommended over revascularization procedures.

2. Ischemic stroke or TIA secondary to cervicocephalic artery dissection

- Clinical markers of cervicocephalic artery dissection include: young age, predisposing connective tissue disease (e.g., Marfan, Ehler-Danlos), and neck trauma or extreme neck movement before stroke or TIA, and head or neck pain preceding ischemic stroke or TIA.
- CT- or MR-angiography is recommended when cervicocephalic artery dissection is suspected.
- There is uncertainty about the efficacy of treatment comparing antiplatelet monotherapy, dual antiplatelet therapy versus anticoagulation for cervicocephalic dissection; treatment with either option is reasonable. The treatment modality (anticoagulation with heparin or warfarin or antiplatelets) should be based on the estimated risks and benefits based on information from clinical features, brain imaging (infarct size, hemorrhagic transformation), vascular imaging (dissection location and severity, intraluminal thrombus), and estimated bleeding risks. Anticoagulant therapy can be considered for secondary prevention in patients with high-risk radiological features (intraluminal thrombus, severe low-flow stenosis to occlusive dissection) and at low bleeding risk. Antiplatelet therapy monotherapy can be considered in patients at high bleeding risk and patients with moderate bleeding risk and no high-risk radiological features.
- The optimal duration of antithrombotic treatment is unknown. Variables such as residual vascular changes, prior or multiple dissections, predisposing conditions are typically considered on an individual basis.

3. Ischemic stroke or TIA secondary to fibromuscular dysplasia (FMD) and no artery dissection

- Antiplatelet agents are recommended for secondary prevention of ischemic stroke or TIA with no identified potential cause other than FMD. Anticoagulation, if indicated for another reason, can be used rather than antiplatelet agents for secondary prevention.
- There is no evidence to support the use of statin drugs in patients with stroke or TIA secondary to FMD, unless otherwise indicated for dyslipidemia or arteriosclerosis.
- Patients who experience recurrent stroke or TIA secondary to FMD despite antithrombotic prophylaxis should be evaluated by a health professional with stroke expertise for consideration to arterial revascularization, generally by endovascular therapy.

4. Ischemic stroke or TIA secondary to moyamoya in adults

- Patients with moyamoya should be referred to highly specialized centers with expertise in moyamoya disease, for consideration to assessment of cerebral hemodynamic compromise and posterior circulation involvement, consideration to revascularization surgery, and long-term clinical and radiological follow-up.
- Antiplatelet agents are generally recommended in patients with ischemic stroke or TIA secondary to non-hemorrhagic moyamoya.
- Revascularization surgery should be considered in patients with ischemic or hemorrhagic presentation, and asymptomatic patients with cerebral hemodynamic impairment and relevant subclinical ischemic lesions. Direct or combined techniques are preferred to indirect surgeries, with an interval of 6 to 12 weeks from the last cerebrovascular event.

5. Ischemic stroke or TIA secondary to patent foramen ovale (PFO)

- Patients with an ischemic stroke or TIA attributed to a PFO should be evaluated without delay by a health professional with stroke and cardiovascular expertise.
- In patients with PFO, clinical markers of causality include: young age, Valsalva maneuver at onset of ischemic stroke or TIA, physiological or cardiopulmonary conditions associated with an increased right-to-left pressure gradient, suspected or documented thromboembolic events, and non-lacunar symptoms.
- Echocardiographic markers of causality include: atrial septal aneurysm, large right-to-left shunt (e.g., >20 microbubbles), and large PFO diameter (≥2 mm).
- Long-term antithrombotic treatment is recommended in patients with ischemic stroke attributed to PFO.
- Antiplatelet therapy and percutaneous PFO closure are recommended in patients aged 18-60 years with a recent non-lacunar ischemic stroke attributed to PFO and exclusion of other causes from a thorough aetiological investigation.
- The benefit of PFO closure for patients requiring long-term anticoagulation for another indication is uncertain.
- It may be reasonable to not proceed with PFO closure for patients who have none of the following higher-risk anatomical features on echocardiography: (a) atrial septal aneurysm; (b) large right-to-left shunt (e.g., >20 microbubbles); and (c) large diameter PFO (e.g., ≥2 mm).

Other Relevant Thrombosis Canada Clinical Guides:

- Acetylsalicylic Acid (ASA)
- Cerebral venous thrombosis
- Cancer and thrombosis
- Clopidogrel (Plavix®)
- Rivaroxaban (Xarelto®)
- Stroke Prevention in Atrial Fibrillation
- Thrombophilia: Antiphospholipid Antibody Syndrome

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