REVIEW ARTICLE

Canadian Stroke Best Practice Recommendations: Secondary Prevention of Stroke Update 2020

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Abstract The 2020 update of the Canadian Stroke Best Practice Recommendations (CSBPR) for the *Secondary Prevention of Stroke* includes current evidence-based recommendations and expert opinions intended for use by clinicians across a broad range of settings. They provide guidance for the prevention of ischemic stroke recurrence through the identification and management of modifiable vascular risk factors. Recommendations address triage, diagnostic testing, lifestyle behaviors, vaping, hypertension, hyperlipidemia, diabetes, atrial fibrillation, other cardiac conditions, antiplatelet and anticoagulant therapies, and carotid and vertebral artery disease. This update of the previous 2017 guideline contains several new or revised recommendations. Recommendations regarding triage and initial assessment of acute transient ischemic attack (TIA) and minor stroke have been simplified, and selected aspects of the etiological stroke workup are revised. Updated treatment recommendations based on new evidence have been made for dual antiplatelet therapy for TIA and minor stroke; anticoagulant therapy for atrial fibrillation; embolic strokes of undetermined source; low-density lipoprotein lowering; hypertriglyceridemia; diabetes treatment; and patent foramen ovale management. A new section has been added to provide practical guidance regarding temporary interruption of antithrombotic therapy for surgical procedures. Cancer-associated ischemic stroke is addressed. A section on virtual care delivery of secondary stroke prevention services in included to highlight a shifting paradigm of care delivery made more urgent by the global pandemic. In addition, where appropriate, sex differences as they pertain to treatments have been addressed. The CSBPR include supporting materials such as implementation resources to facilitate the adoption of evidence into practice and performance measures to enable monitoring of uptake and effectiveness of recommendations.

*Manraj K.S. Heran and Pascale Lavoie have been added as authors; their information has been added to the author affiliations, "Conflicts of Interest," and "Statement of Authorship" sections. Additionally, the supplementary material has been updated with new files. A corrigendum detailing these changes has also been published (doi: 10.1017/cjn.2022.57).

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RÉSUMÉ : La mise à jour 2020 des Recommandations canadiennes pour les pratiques optimales de soins de l'AVC, relatives à la prévention secondaire. La mise à jour 2020 des Recommandations canadiennes pour les pratiques optimales de soins de l'AVC, relatives à la prévention secondaire de ce type de trouble comprend des recommandations fondées sur les dernières données probantes ainsi que des avis d'experts courants, émis à l'intention des cliniciens pratiquant dans divers milieux de soins. Les lignes de conduite présentées dans ces recommandations visent la prévention de futurs accidents vasculaires cérébraux (AVC) ischémiques, et ce, par la reconnaissance et la prise en charge de facteurs de risque vasculaire modifiables. L'équipe de travail s'est ainsi penchée sur le triage, les examens de diagnostic, le mode de vie, le vapotage, l'hypertension, l'hyperlipidémie, le diabète, la fibrillation auriculaire et autres troubles cardiaques, les traitements antiplaquettaire et anticoagulant ainsi que l'atteinte des artères carotides et vertébrales. La mise à jour des lignes directrices de 2017 contient plusieurs recommandations nouvelles ou révisées. Celles relatives au triage et à l'évaluation initiale des accidents ischémiques transitoires (AIT) aigus et des petits AVC ont été simplifiées, et certains aspects du bilan étiologique des AVC, révisés. La mise à jour des recommandations relatives au traitement fondées sur de nouvelles données probantes touche la bithérapie antiplaquettaire pour les AIT et les petits AVC; l'anticoagulothérapie pour la fibrillation auriculaire; les AVC emboliques de cause indéterminée; l'abaissement du taux de LDL; l'hypertriglycéridémie; le traitement du diabète; et la prise en charge de la persistance du foramen ovale. À cela s'ajoute une nouvelle section qui offre des conseils pratiques sur l'arrêt temporaire du traitement antithrombotique en vue d'une intervention chirurgicale. Il est également question des AVC ischémiques associés au cancer. Dans une autre section portant sur la prestation virtuelle des services de prévention secondaire de l'AVC, on fait ressortir un changement de paradigme dans la prestation des soins, changement qui s'est imposé plus que jamais avec la pandémie. Les auteurs ont aussi traité des différences de traitement en lien avec le sexe lorsque c'était pertinent. Enfin se greffent aux nouvelles recommandations des ressources didactiques, par exemple de la documentation sur la mise en œuvre visant à faciliter la transposition des données probantes en des mesures de pratique et de performance afin de rendre possible la surveillance de l'application et de l'efficacité des recommandations.

Keywords: Stroke, Transient ischemic attack, Guidelines, Secondary prevention, Risk assessment, Management

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Introduction

Optimizing stroke prevention is a major public health priority. Stroke remains a leading cause of adult neurological disability (both physical and cognitive), dementia, and death globally. The seventh update of the Canadian Stroke Best Practice Recommendations (CSBPR) *Secondary Prevention of Stroke* guidelines includes a summary of current evidence-based recommendations for healthcare professionals. They focus on reducing the risk of recurrent stroke following an index ischemic stroke or transient ischemic attack (TIA) and are applicable to patients managed across a variety of care settings. They emphasize a coordinated and organized approach to assessment and aggressive risk factor management. The core elements of integrated and effective secondary stroke prevention services are included in the supplemental material, Appendix Four. Patient management aims to identify treatable risk factors, apply evidence-based treatment interventions to minimize risk, provide patient education and shared decision-making, and encourage patient adherence and persistence with treatment recommendations.

These recommendations have been developed in collaboration with the Canadian Stroke Consortium. We collaborate with the Canadian Cardiovascular Society, Thrombosis Canada, Diabetes Canada, and Hypertension Canada to ensure alignment of recommendations wherever possible. Those guidelines should be consulted for additional detail and information beyond the scope of the CSBPR. *The Canadian Stroke Best Practice Recommendations (CSBPR) Secondary Prevention of Stroke 2020 Seventh Edition module supersedes all recommendations contained in the CSBPR Secondary Prevention of Stroke 2017 Sixth Edition module.*

Guideline Development Methodology

The CSBPR development and update process follows a rigorous framework[1,2] and addresses all criteria defined within the AGREE trust model.[3] The methodology for development and updates to the CSBPR has previously published[4,5] and detailed methodology can be found on our Canadian Stroke Best Practices website at www.strokebestpractices.ca. A broad interdisciplinary group of experts was convened and participated in reviewing, drafting, and revising all recommendation statements, and a panel of people with lived experience participated in a parallel review process.[6] Evidence levels were assigned based on the quality of available evidence and expert opinion. These guidelines have undergone extensive internal and objective external review and consensus was achieved for all content. For additional methodology and information on these recommendations, including rationale, system implications, performance measures, knowledge translation and implementation tools, and an extended summary of the evidence, please visit https://www.strokebestpractices.ca/recommendations/secondary-prevention-of-stroke.

Secondary Prevention of Stroke Recommendations

Section 1: Triage and Initial Diagnostic Evaluation of Transient Ischemic Attack and Non-Disabling Stroke

An acute TIA or minor stroke is a medical emergency. Initial management aims to establish an accurate diagnosis, determine the likely etiology, and institute secondary prevention therapy as quickly as possible. Patients with acute TIA or minor stroke are at risk of recurrent stroke both in the short-term (particularly within the first week)[7] and long-term.[8] Our triage recommendations have been simplified to focus on patients presenting within the first 48 h of a suspected new acute TIA or stroke as they are at highest risk of early recurrent stroke. For such patients, immediate assessment is recommended, with imaging of both brain (head computerized tomography [CT] or magnetic resonance imaging [MRI]) and vessels (ideally with a CT angiogram from aortic arch to vertex) on an urgent basis.[9]

An embolic stroke or TIA can be the first manifestation of previously unrecognized atrial fibrillation. We recommend a tiered approach to searching for atrial fibrillation in patients with a new acute embolic ischemic stroke or TIA.[10] The goal of post-stroke electrocardiogram (ECG) monitoring is to detect

high-burden atrial fibrillation for which anticoagulation would likely be beneficial. However, ECG monitoring often reveals brief subclinical paroxysmal atrial fibrillation, and it remains unclear what amount of device-detected atrial fibrillation warrants anticoagulation. Trials underway are evaluating this question. The effect of post-stroke prolonged ECG monitoring on hard clinical outcomes (i.e., recurrent stroke) remains to be determined and is the subject of ongoing research (FIND-AF2 trial, NCT04371055).

Echocardiography can be a valuable tool in the etiological assessment and risk stratification of patients with stroke and TIA. However, it can be overutilized and we recommend responsible use of this resource. Thus, the recommendations emphasize that echocardiography is not required for all stroke patients but should be considered for those with an embolic ischemic stroke or TIA of undetermined source (ESUS) or when a cardioembolic etiology or paradoxical embolism is suspected.

We have recommended against extensive thrombophilia testing for hereditary hypercoagulable disorders in the routine investigation of adults with arterial ischemic stroke events. Such testing is often overused in practice and should be limited to selected patients such as those with unexplained cerebral venous thrombosis or patent foramen ovale-related (PFO) paradoxical embolism.

An important lesson of the COVID-19 pandemic has been how essential remote or virtual contact with patients and families is to providing safe and timely care for stroke patients. In particular, care for patients living in rural or remote communities or patients for whom mobility and transport to clinic or hospital are prohibitive, can be improved via virtual care. Home blood pressure monitoring is encouraged in accordance with Hypertension Canada guidelines.[11] Home delivery of ECG patch monitors that can be self-applied by patients is a welcome option in regions where it is available. Virtual care interventions can be effective for blood pressure lowering, improvements in diet, increased physical activity, drug adherence, and satisfaction with access to care,[12] reduced HgbA1c, smoking cessation,[13] and reduced risk of cardiovascular events.[14]

Section 1 Recommendations 2020

1.0 Patients with acute stroke or transient ischemic attack (TIA) who present to an ambulatory setting (such as primary care) or a hospital should undergo clinical evaluation by a healthcare professional with expertise in stroke care to determine risk for recurrent stroke and initiate appropriate and timely investigations and management strategies.

1.1 HIGH Risk for Recurrent Stroke (Symptom onset within last 48 h)

i. Individuals presenting within 48 h of symptoms consistent with a new acute stroke or TIA event (especially transient focal motor or speech symptoms, or persistent stroke symptoms) are **at the highest risk for recurrent stroke** and should be immediately sent to an emergency department (refer to Clinical Consideration 1.1.3) with capacity for stroke care (including onsite brain imaging, and ideally access to acute stroke treatments) [Evidence Level B].
ii. Urgent brain imaging (CT or MRI) with concurrent neurovascular imaging (e.g., CT angiography [CTA]) should be completed as soon as possible and before discharge from the emergency department [Evidence Level B].
iii. Patients presenting after 48 h from the onset of an acute stroke or TIA event should receive a comprehensive clinical evaluation and investigations as soon as possible by a healthcare professional with stroke expertise [Evidence Level B].

Section 1.1 Clinical Considerations:

1. Referral to a healthcare professional with expertise in stroke care should be considered for patients with a suspected uncommon cause of stroke, including for young stroke patients (e.g., <45 years);[15] family history of young-onset stroke; suspected cerebral vasculitis or other intracranial vasculopathy; or suspected hereditary or acquired thrombophilia.
2. Patients presenting with symptoms of vertebrobasilar ischemia may present with fluctuating brainstem/cerebellar type symptoms (e.g., diplopia, dysarthria, dysphagia, non-positional vertigo, ataxia; rarely as isolated symptoms) over a longer time course (i.e., more than 48 h) and can be mistaken for stroke mimics; however, they also require urgent assessment, neurovascular imaging and management as these types of strokes can have a high morbidity. Consultation with a healthcare professional with expertise in stroke care is strongly encouraged.
3. Setting: In some regions, urgent/rapid TIA clinics are available that have rapid access to diagnostic services, and they may be considered as appropriate referral options for TIA and minor stroke patients where available and accessible.

1.2 Brain and Vascular Imaging

i. Brain imaging (CT or MRI) and non-invasive vascular imaging (CTA or MR Angiogram [MRA] from aortic arch to vertex) should be completed as soon as possible following acute stroke or TIA [Evidence Level B].
   a. CTA of head and neck (from aortic arch to vertex), which can be performed at the time of initial brain CT, is recommended as an ideal way to assess both the extracranial and intracranial circulation [Evidence Level B]. *Note: Some facilities may not have CTA readily available; the timing and type of vascular imaging will need to be based on available resources and local practice protocols.*
   b. Neurovascular imaging is recommended to identify patients with significant symptomatic extracranial carotid artery stenosis (i.e., 50%–99% stenosis), which should trigger an urgent referral for potential carotid revascularization [Evidence Level A].
   c. CTA is the first-line vascular imaging test for stroke/TIA patients. MRA and carotid ultrasound (for extracranial vascular imaging) are reasonable alternatives to CTA as first-line tests for assessment of carotid vessels if CTA is not possible, and selection should be

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based on availability and patient characteristics [Evidence Level C].

Section 1.2 Clinical Considerations:

1. Brain MRI is superior to a head CT scan in terms of diagnostic sensitivity for identifying small ischemic lesions in patients presenting clinically with a TIA or minor stroke event and can provide additional information for guiding diagnosis, prognosis, and treatment decision-making. Decisions regarding MRI scanning should be based on MRI access, availability, and timing of appointments. For maximal diagnostic yield, MRI should be completed as soon as possible after the symptomatic event, ideally within 7 d of symptom onset. MRI is particularly useful in lower risk patients with transient symptoms in whom the presence of ischemia would change their management.
2. Common scenarios where urgent brain MRI can be valuable include:
   a. Normal CT head despite symptoms persisting >24 h (if diffusion-weighted imaging [DWI]-MRI is negative, cerebral ischemia is unlikely).
   b. Suspected brainstem or cerebellar ischemia (CT head is insensitive for detecting strokes in the posterior fossa due to bone artifact).
   c. Focal transient symptoms that are clinically atypical for ischemia.

1.3 Blood Work

i. The following laboratory investigations should be routinely considered for patients with a TIA or minor ischemic stroke as part of the initial evaluation:
   a. **Initial bloodwork**: hematology (complete blood count), electrolytes, coagulation (aPTT, INR), renal function (creatinine, estimated glomerular filtration rate), random glucose, ALT [Evidence Level C]. *Refer to Appendix Two for full list of recommended lab tests.*
   b. **Additional** laboratory tests may be completed during patient encounter or as an outpatient, including a lipid profile (fasting or non-fasting); and screening for diabetes with either a glycated hemoglobin (HbA1c), fasting glucose or 75 g oral glucose tolerance test [Evidence Level C].
   c. **(New for 2020):** If giant cell arteritis is suspected (e.g., retinal ischemia or headache), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) should be measured [Evidence Level C].

ii. **(New for 2020):** Extensive thrombophilia testing for hereditary hypercoagulable disorders is not recommended for routine investigation of a patient with arterial ischemic stroke and should be limited to selected situations (e.g., but not limited to, unexplained cerebral venous thrombosis; PFO-related paradoxical embolism) [Evidence Level C].
   a. If a hypercoagulable state is suspected, consider consultation with a healthcare professional with hematology or thrombosis expertise [Evidence Level C].

1.4 Cardiac Studies

1.4A Detection of Atrial Fibrillation

i. Patients with suspected ischemic stroke or TIA should have a 12-lead ECG to assess for atrial fibrillation, concurrent myocardial infarction, or structural heart disease (e.g., left ventricular hypertrophy) as potential causes or risk factors of stroke [Evidence Level B].
ii. For patients being investigated for an acute embolic ischemic stroke or TIA, ECG monitoring for 24 h or more is recommended as part of the initial stroke work-up to detect paroxysmal atrial fibrillation in patients who would be potential candidates for anticoagulant therapy [Evidence Level A].
iii. For patients being investigated for an embolic ischemic stroke or TIA of undetermined source whose initial short-term ECG monitoring does not reveal atrial fibrillation but a cardioembolic mechanism is suspected, continuous ECG monitoring for at least 2 weeks is recommended to improve detection of paroxysmal atrial fibrillation in selected patients aged ≥55 years who are not already receiving anticoagulant therapy but who would be potential candidates for anticoagulant therapy [Evidence Level A].
iv. **(New for 2020):** For patients aged >65 years with ischemic stroke or TIA, pulse palpation or heart auscultation or ECG rhythm strip is recommended to screen for undiagnosed atrial fibrillation [Evidence Level B].

1.4B Echocardiography

i. Echocardiography should be considered for patients with an embolic ischemic stroke or TIA of undetermined source or when a cardioembolic etiology or paradoxical embolism is suspected [Evidence Level C]. Routine echocardiography is not required for all stroke patients. [Evidence Level C].
ii. **(New for 2020):** For patients aged 60 years or younger who are being investigated for an embolic ischemic stroke or TIA of undetermined source, echocardiography with saline bubble study is recommended for detection of a possible PFO if it may change patient management (i.e., in patients who would be potential candidates for PFO closure or anticoagulant therapy if a PFO were detected) [Evidence Level B].
   a. Contrast-enhanced (agitated saline) transesophageal echocardiography or transcranial Doppler has greater sensitivity than transthoracic echocardiography for detection of right-to-left cardiac and extra-cardiac shunts [Evidence Level B].

1.5 Functional Assessment:

i. Patients with stroke should be assessed for neurological impairments and functional limitations (e.g., cognitive evaluation, screening for depression, screening for dysphagia, screening of fitness to drive, need for potential

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rehabilitation therapy, and assistance with activities of daily living) [Evidence Level B].

ii. Patients found to have neurological impairments and functional limitations should be considered for referral to the appropriate rehabilitation specialist for in-depth assessment and management [Evidence Level B].

1.6 Virtual Care for Secondary Stroke Prevention (New 2020)

i. Secondary stroke prevention services should establish processes and technology to increase and ensure access to services through virtual care delivery mechanisms for patients who do not require in-person visits, and especially patients living in rural and remote settings without local access to healthcare professionals with stroke expertise [Evidence Level C].
   a. Clinicians should follow established/validated criteria to determine the best modality for each patient at each encounter based on the purpose and goals for each visit [Evidence Level C].
   b. Shared decision-making should also take into account patient values, preferences, health goals, medical complexity, social determinants of health, and health needs [Evidence Level C].

Section 1.6 Clinical Considerations:

1. Consulting sites and individual clinicians should have triage protocols and local intake criteria in place to ensure patients referred for their services are seen in a timely manner, especially high-risk patients as described in section 1.1 of this module.
2. The use of virtual care for stroke prevention should include decision tools to identify patients who require in-person visits and those who can reasonably be managed through virtual care, and a scheduling mechanism for virtual visits that support a collaborative team approach to care where appropriate and feasible.
3. A contingency plan should be established to have patients seen in person in a timely way should the need arise following a virtual care encounter.
4. Virtual care-enabled evaluations of patients for secondary stroke prevention should be modeled on the topics defined in the post-stroke checklist and core elements of stroke prevention care.
5. Validated approaches to virtual neurological exams should be followed.
6. Barriers to access, equity, and utilization should be considered and work-around solutions implemented.
7. Ensure processes in place for booking follow-up tests, referrals, and other consultations following a virtual care visit.
8. Ensure appropriate documentation and communication to other team members who may also be involved in care remotely.
9. Encourage patients and their families to acquire home blood pressure monitors where appropriate and provide education or reliable resources on proper use. Mechanisms should be in place for follow-up and management of BP for patients using home BP devices, by either primary care providers or Stroke Prevention Services (SPS).
10. For timely investigations, consider use of prolonged cardiac monitors, if available, that can be sent to patient's homes and self-applied, then returned by mail.
11. Data collection and quality improvement mechanisms should be in place to monitor efficiency, effectiveness, and quality of virtual care encounters.

Section 2: Lifestyle Behaviors and Risk Factor Management

A healthy lifestyle, which includes a Mediterranean or Dietary Approaches to Stop Hypertension (DASH) diet, exercise, weight control, reduction, and avoidance of alcohol and tobacco, reduces the risk of an initial stroke and the risk of a subsequent stroke for patients with a prior history of stroke. Although individually, these habits can reduce the risk of stroke, their impact is greater when combined. Even greater impacts can be achieved with population level interventions for physical activity include investments in health promoting infrastructure (e.g., sidewalks, walking paths, bike lanes). At the core of these of interventions is a focus on making the healthy choice the easy choice.

Section 2 Recommendations 2020
2.1 Risk Factor Assessment:

i. Persons at risk of stroke and patients who have had a stroke or TIA should be assessed for vascular disease risk factors, lifestyle management issues (diet, sodium intake, exercise, weight, alcohol intake, smoking), as well as use of oral contraceptives or hormone replacement therapy [Evidence Level B].

ii. Persons at risk of stroke or TIA and their family members should receive individualized information and counselling about possible strategies to modify their lifestyle and vascular risk factors [Evidence Level B].

iii. Referrals to appropriate specialists should be made to support and manage specific vascular risk factors and lifestyle behaviors and choices where required [Evidence Level B].

2.2 Healthy Balanced Diet

i. Counsel and educate individuals with TIA or stroke to follow a healthy eating pattern and balanced diet [Evidence Level B] or refer to a registered dietitian where available [Evidence Level C].

ii. Counsel and educate individuals with TIA or stroke to follow a Mediterranean-type or Dietary Approach to Stop Hypertension (DASH) diet, which is high in vegetables, fruit, whole grains, fish, nuts and olive oil and low in red meat [Evidence Level B].

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iii. Counselling may include:
   a. consuming a variety of natural, whole, and minimally processed foods at each meal [Evidence Level B].
   b. consuming fewer highly processed foods, which include refined foods, confectionaries, sugary drinks, processed meats and meat alternatives, and pre-prepared foods [Evidence Level B].
   c. consuming a diet high in vegetables and fruit; encourage patients to choose fresh or frozen unsweetened fruit, or fruit canned in water without added sugars and low in sodium; fresh or frozen vegetables without added sauces, or canned vegetables with no added salt [Evidence Level B].
   d. consuming lower fat and lower sugar dairy products and unsweetened fortified soy beverages [Evidence Level B].
   e. shift to consuming more protein from plant-based sources (legumes, nuts, and seeds) and other protein options which are lower in saturated fats such as fish, poultry, and lean meats [Evidence Level B].
   f. consuming high fiber choices such as whole grains, beans, and legumes instead of processed or refined grains such as white bread and pasta [Evidence Level B].
   g. consuming water as the drink of choice for hydration. Sugary drinks (such as energy drinks, fruit drinks, juice, soft drinks, and flavored coffees) add calories and have little to no nutritional value and should be discouraged [Evidence Level A].
   h. consuming foods low in sodium [Evidence Level B].

Section 2.2 Clinical Consideration

1. Counsel and educate individuals regarding healthy eating patterns that focus on whole, natural, minimally processed foods, instead of specific nutrients such as dietary cholesterol.

2.3 Sodium Intake

i. To prevent hypertension and to reduce blood pressure in patients with hypertension, counsel and educate individuals with TIA or stroke to reduce sodium intake to a goal of no more than 2000 mg (5 g table salt or 87 mmol sodium, equal to less than one teaspoon) per day [Evidence Level A].

Section 2.3 Clinical Consideration

i. Achieving a sodium intake of <2000 mg may be very difficult for the general population and average daily intake among people in Canada is 2760 mg. Encourage a gradual decrease in foods that are high in sodium which will allow taste buds and behavior to adapt appropriately.

2.4 Physical Activity

i. Counsel and educate individuals with TIA or stroke to reduce sedentary behaviors and sedentary time, and to work toward increased activity goals as tolerated [Evidence Level B].
ii. Most individuals post-stroke who are medically stable should start a regular exercise program [Evidence Level B].
iii. Counsel and educate individuals with TIA or stroke to participate in aerobic exercise 4 to 7 d per week, to accumulate at least 150 min per week in episodes of 10 min or more, in addition to routine activities of daily living [Evidence Level B].
iv. Initiation of aerobic training should be considered after a stroke or TIA once the patient is medically stable. To ensure continuity of appropriate interventions, patients should be reassessed at transition points along the continuum of care based on changing neuromotor and cardiopulmonary capacities to participate in aerobic training [Evidence Level B].

Section 2.4 Clinical considerations

1. Aerobic exercise intensity should be individualized. Factors to consider include functional limitation, coexisting medical problems such as cardiac disease, need for an exercise stress test with electrocardiogram, and planned exercise intensity (i.e., light, moderate, or vigorous).
2. Screening and supervision of adults with comorbid disease such as cardiac disease which places them at higher risk of medical complications should be considered.
3. Supervision by a healthcare professional (such as a physiotherapist) at exercise initiation should be considered in individuals with stroke at risk of falls or injury.

2.5 Weight Management

i. Counsel and educate individuals with TIA or stroke to achieve and maintain a waist circumference of <88 cm for women and <102 cm for men*, or a body mass index (BMI) of 18.5–24.9 kg/m2 [Evidence Level B]. (**Note: these numbers are reflective of current research based mostly on Caucasian patients. Refer to Reference list for waist circumference values for other ethnic groups.*)
ii. Counsel and educate individuals with TIA or stroke who are overweight to set healthy weight loss goals and develop individualized plans to achieve goals [Evidence Level B].
iii. A multi-pronged approach should be used to support sustainable weight loss or weight gain that includes counselling and education, increased physical activity, and behavioral interventions [Evidence Level B].

Section 2.5 Clinical Consideration

1. When discussing weight, consider completion of a comprehensive history that explores root causes of weight gain and avoids stigma and judgment.

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2.6 Alcohol Consumption

i. Counsel and educate individuals with TIA or stroke to avoid heavy alcohol use as excessive alcohol intake increases the risk of hypertension, ischemic stroke and intracerebral hemorrhage. [Evidence Level B].
ii. Counsel and educate individuals with TIA or stroke to follow Canada's Low-Risk Alcohol Drinking Guidelines (2018): for women, no more than 10 drinks per week, with no more than 2 drinks per day most days, and no more than 3 drinks on any single occasion; for men, no more than 15 drinks per week, with no more than 3 drinks per day most days, and no more than 4 drinks on any single occasion [Evidence Level B].
Note: one standard drink is considered to be approximately 44 mL (1.5 oz) of 80 proof (40%) spirits, 355 mL (12 oz) of 5% beer or 148 mL (5 oz) of 12% wine.

2.7 Recreational Drug Use

i. Individuals with stroke and known recreational drug use that may increase the risk of stroke (such as cocaine, amphetamines) should be counseled to discontinue use [Evidence Level C]; and should be provided with appropriate support and referrals to services and resources for drug addiction and rehabilitation [Evidence Level B].
ii. For cannabis, that may be prescribed for medical indications, counsel patients regarding any potential increased risk of stroke to support informed decision-making regarding the use of these agents [Evidence Level B].

Section 2.7 Clinical Consideration

1. At present, there has been some association of smoking cannabis products with possible increased stroke and cardiovascular events. However, there is a lack of high-quality evidence to provide clear guidance. Individual patient factors should be considered.

2.8 Smoking Cessation

Note, the term "Smoking" in these recommendations refers to tobacco and other inhaled substances.

i. In all healthcare settings along the stroke continuum (inpatient, ambulatory, and community), patient smoking status should be identified, assessed, and documented [Evidence Level A].
ii. Provide unambiguous, non-judgmental, and patient-specific advice regarding the importance of cessation to all smokers [Evidence Level B] and others who reside with the patient.
iii. Offer assistance with the initiation of a smoking cessation attempt – either directly or through referral to appropriate resources [Evidence Level A].
iv. A stepwise approach that starts with reduction in smoking and progresses to full cessation is a valid approach [Evidence Level B].
v. A combination of pharmacotherapy and behavioral therapy should be considered in all smoking cessation programs and interventions [Evidence Level A].
vi. The three classes of pharmacological agents that should be considered as first-line therapy for smoking cessation are nicotine replacement therapy, varenicline, and bupropion [Evidence Level A].
    a. The choice of appropriate pharmacotherapy should take into account the patient's medical stability, clinical needs, other medical factors, patient preferences, and patient's ability to afford the therapy in those cases in which it is not covered under a provincial drug formulary [Evidence Level C].
    b. The initiation of pharmacotherapy for smoking cessation should begin as soon as possible and supported while in hospital for index stroke-related event [Evidence Level C]. Earlier initiation of smoking cessation discussions may be beneficial [Evidence Level C].
vii. For stroke patients in hospital who are current smokers, protocols should be in place to manage nicotine withdrawal during hospitalization [Evidence Level B].
viii. Interdisciplinary team members should counsel patients, family members, and caregivers about the harmful effects of exposure to environmental (second hand) smoke [Evidence Level B].
ix. A referral to virtual smoking cessation services, smoking cessation programs, supportive resources, and clinics should be considered depending on regional availability to optimize the success of smoking cessation [Evidence Level B]
x. People who are not ready to quit should be offered a motivational intervention to help enhance their readiness to quit [Evidence Level B].

Section 2.8 Clinical Considerations
Use of E-Cigarettes

1. Although some individuals may find vape products helpful in smoking cessation, the evidence base around their population-based effectiveness is not clear.
2. There is some evidence that shows people who use vaping as a mechanism to quit cigarettes may continue to vape even after cessation of cigarette use, in contrast to use of nicotine replacement therapy which has not been found to be continued in an ongoing basis.[16]
3. Emerging evidence indicates an association between vaping and elevated blood pressure; the strength of the association is not clear at this time.
4. The most common pattern of use in Canada is dual use of both vape and combustible tobacco products and therefore smoking cessation strategies should include consideration for both methods of nicotine consumption.
5. Education and counselling should be provided regarding the risks versus benefits of e-cigarettes in people with stroke, including in younger age groups who have experienced stroke.

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2.9 Pregnancy, Oral Contraceptives, and Hormone Replacement Therapy

i. Discussions of pregnancy and implications for stroke recurrence should be included as a routine part of post-stroke management for all female stroke survivors of reproductive age [Evidence Level C].
ii. Contraception should be addressed based upon the patients' fertility and pregnancy plans as well as the stroke mechanism and type [Evidence Level C].
iii. In cases of ischemic stroke, systemic estrogen-containing contraceptives or hormone replacement therapy that can increase the risk of thrombosis should be carefully considered and, in most cases, should be avoided due to an increased risk of stroke [Evidence Level B].
iv. Management alternatives, including progesterone-only oral contraceptives, progesterone-only or non-hormonal intrauterine devices, or barrier contraception can be considered in consultation with a provider experienced with contraceptive methods [Evidence Level C].
v. Estrogen-containing oral contraceptives or hormone replacement therapy should be discouraged or discontinued in female patients with TIA or ischemic stroke [Evidence Level B]. Management alternatives should be considered in these patients [Evidence Level C].
vi. **(New for 2020)** Contraceptive management alternatives to estrogen containing hormonal contraceptives should be considered for women with a history of migraine with aura [Evidence Level C], especially if they are also current tobacco smokers [Evidence Level B].[17]
vii. **Hypertensive Disorders of Pregnancy**: Discussion on the use and dose of acetylsalicylic acid (ASA) to reduce the risk of a hypertensive disorder of pregnancy (HDP) should be individualized based upon a woman's risk of HDP (i.e., women with a prior ischemic stroke, prior HDP or other risk factors) and in consultation with obstetrical care providers [Evidence Level C]. *Refer to CSBPR Stroke during Pregnancy recommendations for additional information.*
viii. **Invitro Fertilization**: For women who have had a cerebral event and are considering invitro fertilization, provide counselling and education about risks of fertility therapy including the potential risk of hyperstimulation, and monitor for complications assuming all other stroke in the young management plans followed and optimized [Evidence Level C].

2.10 Adherence to individual prevention plans

i. At each healthcare encounter, discuss and document patient adherence to their prescribed secondary prevention treatment plans (pharmacotherapy and lifestyle changes), explore and address non-adherence, and provide counselling and engage in joint goal setting to encourage adherence and persistence with treatment [Evidence Level C].

2.11 Emerging Risk Factors
Influenza infection, vaccination, and stroke risk

i. Influenza vaccination is recommended as it has been shown to be associated with a decreased risk of stroke or cardiovascular events, particularly in patients with pre-existing cardiovascular risk factors [Evidence Level B].

Air pollution and stroke risk

i. Counsel individuals regarding long-term exposure to air pollutants, particularly avoiding or minimizing exposure to particulate matter ≤ 2.5 µm in diameter, which may be associated with an increased risk of stroke and cardiovascular disease [Evidence Level B].

Section 3: Blood Pressure and Stroke Prevention

Hypertension is the major modifiable risk factor for stroke. In Canada, systolic hypertension is estimated to account for about 45% of the total stroke burden.[18] Although the optimal target blood pressure to prevent a first or recurrent stroke has not been formally established, the current treatment recommendation to attain a blood pressure of consistently lower than 140/90 mm Hg for people who have had an ischemic stroke or TIA, can help to reduce recurrent events. Using the results from a subset of 13 randomized controlled trials (RCTs) that included persons with a previous history of stroke, Law et al.[19] reported that blood pressure treatment resulting in a reduction of 10 mm Hg systolic and 5 mm Hg diastolic was associated with a 34% reduced risk of recurrent stroke (RR = 0.66, 95% CI 0.56–0.79). In the RESPECT trial,[20] persons with a history of stroke within the previous 30 d to three years who were randomized to a standard treatment group with a target of <140/90 mm Hg or an intensive treatment group with a target of <120/80 mm Hg, did not have a significantly reduced risk of recurrent stroke (HR = 0.73, 95% CI 0.49–1.11, $p = 0.15$); however, when these results were incorporated into an updated meta-analysis, the risk was reduced significantly with intensive therapy. The number needed to treat to prevent one recurrent stroke was 67, with an absolute risk reduction of 1.5%.

Section 3 Recommendations 2020
3.0 Blood pressure should be assessed and managed in all persons with stroke or TIA [Evidence Level A].

3.1 Blood pressure assessment

i. All persons at risk of recurrent stroke should have their blood pressure measured routinely [Evidence Level A], no less than once annually and more frequently based on individual clinical circumstances [Evidence Level C].
ii. Proper standardized techniques should be followed for initial and subsequent blood pressure measurement including office, home, and community testing [Evidence Level B] as outlined by the Hypertension Canada Guidelines.

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iii. Patients found to have an automated office measured resting elevated blood pressure (systolic greater than 135 mm Hg and/or diastolic greater than 85 mm Hg) should undergo thorough assessment for the diagnosis of hypertension [Evidence Level C].
   a. During an office visit for assessment of hypertension consider taking the average of three blood pressure measurements conducted in accordance with the current Hypertension Canada Guidelines [Evidence Level C]. *Refer to Hypertension Canada Algorithm for Diagnosis of Hypertension, including Home Blood Pressure Monitoring Targets.*

iv. Patients with refractory hypertension should have comprehensive investigations for secondary causes of hypertension [Evidence Level B].

v. Patients with hypertension or at risk for hypertension (in pre-hypertension state or other risk factors) should receive aggressive risk factor modification, lifestyle counselling, and lifestyle modification interventions [Evidence Level B].

3.2 Blood pressure management

i. Strong consideration should be given to the initiation of antihypertensive therapy after the acute phase of a stroke or TIA [Evidence Level A].

ii. For patients **who have had an ischemic stroke or TIA**, blood pressure lowering treatment is recommended to achieve a target of consistently lower than 140/90 mm Hg [Evidence Level B]; this includes individuals with chronic kidney disease.

iii. For patients **who have had a small subcortical stroke (i.e., lacunar stroke),** aggressive blood pressure lowering treatment is reasonable to achieve a systolic target of consistently lower than 130 mm Hg [Evidence Level B].

iv. **In patients with intracerebral hemorrhage**, blood pressure should be aggressively monitored, treated, and controlled [Evidence Level A] to sustain a target blood pressure consistently lower than 130/80 mm Hg [Evidence Level B]. *Refer to Canadian Stroke Best Practice Recommendations: Management of Intracerebral Hemorrhage module.*

v. **In patients with stroke and diabetes**, blood pressure lowering treatment is recommended for the prevention of first or recurrent stroke to attain a target systolic blood pressure consistently lower than 130 mm Hg [Evidence Level C] and a target diastolic blood pressure consistently lower than 80 mm Hg [Evidence Level A].

vi. Randomized controlled trials have not defined the optimal time to initiate blood pressure lowering therapy after an acute stroke or TIA. Blood pressure lowering treatment should be initiated or modified before discharge from hospital [Evidence Level B].

vii. Treatment with an angiotensin-converting enzyme (ACE) inhibitor and thiazide/thiazide-like diuretic combination is recommended [Evidence Level A]. Long-acting diuretics may be considered over short-acting [Evidence Level B].*

viii. The use of an ACE inhibitor combined with an angiotensin II receptor blockers (ARB) is not recommended [Evidence Level B].*

ix. Patients who are not started on antihypertensive therapy in acute care should have arrangements made for follow-up with primary care or stroke prevention service for ongoing evaluation and management [Evidence Level C]. *Note: Blood pressure management is the responsibility of all healthcare team members, and initially stroke patients may require frequent monitoring (e.g., monthly) until they achieve target blood pressure levels and optimal therapy has been established.*

*Notes: *For recommendations on specific agents and sequence of agents in blood pressure management for the secondary prevention of ischemic stroke, refer to the current Hypertension Canada treatment guidelines*[11]

Section 3 Clinical Considerations

1. **(New for 2020)** For patients with a non-revascularized critical intracranial or extracranial arterial stenosis who are experiencing neurological symptoms attributed to hemodynamic (low flow) cerebral or retinal ischemia (e.g., orthostatic TIAs), it is reasonable to aim for higher than usual blood pressure targets (i.e., permissive hypertension), and avoidance of hypotension, for prevention of hemodynamic stroke; if such patients are asymptomatic, then usual blood pressure targets should be followed in the post-acute phase of stroke.

Section 4: Lipid Management

New evidence supports more aggressive lipid management for secondary stroke prevention. The recommended target low-density lipoprotein (LDL) cholesterol level has been lowered to <1.8 mmol/L, from previously recommended targets of LDL < 2.0 mmol/L or 50% LDL reduction. If this target cannot be achieved with maximum tolerated statin therapy, ezetimibe or a PCSK9 inhibitor may be added for ischemic stroke patients with atherosclerotic disease. Clinicians are reminded that lipid lowering therapies are not recommended for secondary prevention of intracerebral hemorrhage, or for patients with cardioembolic ischemic stroke (e.g., atrial fibrillation) in the absence of atherosclerotic disease.

The Treat Stroke to Target trial studied 2860 patients with atherosclerotic disease who had an ischemic stroke within the previous 3 months or a TIA within the previous 15 d. Treatment to an LDL cholesterol target <1.8 mmol/L, as compared to a target of 2.3–2.8 mmol/L, was associated with a lower risk of major cardiovascular events over a median of 3.5 years (8.5% vs. 10.9%, HR = 0.78, 95% CI 0.61–0.98; $p = 0.04$).[21] About a third of patients in this study required the addition of ezetimibe to their high-dose statin to achieve the more aggressive LDL target.

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Treatment of hypertriglyceridemia with icosapent ethyl 2 g bid may be considered for patients with ischemic stroke who have established atherosclerotic cardiovascular disease, or diabetes plus additional vascular risk factors, and elevated serum triglycerides (≥1.5 mmol/L) despite statin therapy.

Section 4 Recommendations 2020

4.0 Individuals who have had an ischemic stroke or TIA should have their serum lipid levels assessed and optimally managed [Evidence level A].

4.1 Lipid Assessment

i. Lipid levels, including total cholesterol, triglycerides, low-density lipoprotein [LDL] cholesterol, and high-density lipoprotein [HDL] cholesterol, should be measured in patients presenting with ischemic stroke or TIA [Evidence Level B]. *Refer to* Appendix Two *for more information on laboratory tests.*

4.2 Lipid Management

i. Individuals with ischemic stroke or TIA should be managed with aggressive lifestyle changes to lower lipid levels, including dietary modification and exercise, as part of a comprehensive approach to lower risk of recurrent stroke and other vascular events unless contraindicated [Evidence Level B].
ii. Statin pharmacotherapy should be prescribed for secondary prevention of stroke in individuals who have had a non-cardioembolic ischemic stroke or TIA, [Evidence Level A].
   a. A target LDL cholesterol level of <1.8 mmol/L is recommended [Evidence Level B].
iii. Statin therapy should not be initiated for secondary prevention of intracerebral hemorrhage [Evidence Level C].[22]
iv. **Add-on therapies for LDL-Lowering (New 2020):**
   a. For individuals with ischemic stroke and atherosclerotic cardiovascular disease with an LDL > 1.8 mmol/L in spite of maximal tolerated statin therapy, ezetimibe may be considered for additional LDL lowering [Evidence Level B].
   b. For individuals with concomitant atherosclerotic cardiovascular disease in which target LDL level is not achievable, consider referral to a health professional with expertise in metabolic and lipid management, or stroke expertise for consideration of **adding PCSK9 inhibitor** [Evidence Level A].
v. **Add-on therapies for hypertriglyceridemia (New 2020)** For ischemic stroke patients with established atherosclerotic cardiovascular disease or diabetes plus additional vascular risk factors, who have elevated serum triglyceride levels (≥1.5 mmol/L) despite statin therapy, icosapent ethyl 2 g bid may be considered to decrease the risk of vascular events [Evidence Level B].

4.3 Statin Intolerance (New 2020)

i. For patients with an intolerance to statins (including persistent myalgias, persistent significant liver enzyme abnormalities or rarely, myopathy or rhabdomyolysis), the indication for statin therapy should be confirmed and in general, systematic evaluation of the contribution of statins to the patient's symptoms should be considered (including temporary statin cessation with observation of symptoms, dose-adjustment, use of alternate agents) [Evidence Level C]

Section 5: Diabetes Management in Stroke

In Canada, almost 2.5 million people have type 1 or 2 diabetes.[23] Diabetes is known to increase the risk of ischemic stroke by 227%.[24]Although tighter glycemic control along with other risk factor reduction strategies, can collectively help to reduce stroke risk, on its own, aggressive glycemic control does not reduce stroke risk.[25,26] However, trials of newer antihyperglycemic agents, including SGLT-2 and GLP-1 receptor agonists, have demonstrated benefit for major cardiovascular outcomes, including stroke.[27–31]

Section 5 Recommendations 2020

5.0 Patients with diabetes who have had an ischemic stroke or TIA should have their diabetes assessed and optimally managed [Evidence Level A].

5.1 Diabetes Screening and Assessment

i. Patients with ischemic stroke or TIA should be screened for diabetes with either a fasting plasma glucose, or 2-h plasma glucose, or glycated hemoglobin (A1C), or 75 g oral glucose tolerance test in either an inpatient or outpatient setting [Evidence Level C].
ii. For patients with diabetes and either ischemic stroke or TIA, glycated hemoglobin (A1C) should be considered as part of a comprehensive stroke assessment [Evidence Level B].

5.2 Diabetes Management

i. Glycemic targets should be individualized to achieve:
   a. In general, A1C values should be targeted to ≤7.0% in patients with either type 1 or type 2 diabetes (and stroke or TIA), as this target provides strong benefits for the prevention of microvascular complications [Evidence Level A].
   b. To achieve a target of A1C ≤7.0%, most patients with type 1 or type 2 diabetes should aim for a fasting plasma glucose or pre-prandial plasma glucose target of 4.0–7.0 mmol/L [Evidence Level B].
   c. The 2-h postprandial plasma glucose target is 5.0–10.0 mmol/L [Evidence Level B].

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d. If A1C targets cannot be achieved with a postprandial target of 5.0–10.0 mmol/L, further postprandial blood glucose lowering, to 5.0–8.0 mmol/L, should be considered [Evidence Level C].

ii. **(New 2020)** In patients with stroke and type 2 diabetes in whom glycemic targets are not achieved with standard oral antihyperglycemic medications, an antihyperglycemic agent with demonstrated benefit on major cardiovascular outcomes (e.g., SGLT-2 inhibitors or GLP-1 receptor agonists) should be considered [Evidence Level B].

Section 5.2 Clinical Consideration (New 2020):

1. The *Pioglitazone after Ischemic Stroke or TIA* trial[32] suggested that while there is a benefit of pioglitazone for stroke prevention in patients with positive insulin resistance, it is offset by the increased risk of fractures and bladder cancer. A post-hoc analysis of patients in the trial with prediabetes and good drug adherence suggested a benefit of pioglitazone over placebo with regards to stroke, acute coronary syndrome, stroke/myocardial infarction (MI)/hospitalization for heart failure, and progression to diabetes. The decision to use this agent could be considered based on the specific risk profile for each patient.

Section 6.0: Antiplatelet Therapy for Individuals with Ischemic Stroke or TIA

Short-term administration of dual antiplatelet therapy with aspirin and clopidogrel is recommended for secondary stroke prevention, starting within 24 h for eligible patients with acute non-hemorrhagic high-risk TIA or minor ischemic stroke based on the POINT,[33] CHANCE,[34] and FASTER[35] trials. The optimal duration of dual antiplatelet therapy has been clarified by additional analyses[36,37] with net benefit of dual antiplatelet therapy over aspirin alone likely confined to the first 21 d post-TIA/stroke (maximal within the first 10 d). Compared with aspirin, the short-term dual antiplatelet therapy protocol prevents 20 more strokes (and causes two major bleeds) for every 1000 patients treated. Pharmacogenetic testing can identify patients with clopidogrel resistance, however, its clinical implications for stroke prevention practice are unclear at this time.[38–40]

Another short-term dual antiplatelet treatment option is the combination of daily low-dose aspirin and ticagrelor, a P2Y12 antagonist most often used in coronary artery disease. The Acute Stroke or Transient Ischemic Attack Treated With Ticagrelor and ASA for Prevention of Stroke and Death (THALES) trial tested a 30-d course of the aspirin–ticagrelor combination starting within 24 h of a high-risk TIA or minor ischemic stroke.[41] Ticagrelor was administered as a 180 mg loading dose followed by 90 mg twice daily, along with aspirin 75–100 mg daily. This combination reduced the risk of recurrent stroke or death compared with aspirin alone, although the risk of severe bleeding, intracranial bleeding, and fatal bleeding was higher in the ticagrelor–aspirin group. Maximum benefit was observed in patients with ipsilateral large vessel atherosclerotic disease.[42]

The defining features of ESUS are an acute brain infarct visualized on neuroimaging (not a subcortical lacune <1.5 cm); absence of proximal atherosclerotic vessel stenosis >50%; no atrial fibrillation or other major risk cardioembolic source; and no other likely cause for the stroke.[43] Patients with ESUS have an average annual stroke recurrence risk of approximately 5%. Two trials published since the last edition investigated whether patients with ESUS would benefit more from anticoagulation than aspirin. Neither trial showed found a significant reduction in recurrent stroke risk and therefore anticoagulation is not recommended for patients with ESUS.[44,60] The lack of an overall benefit of anticoagulation likely reflects that ESUS comprises a heterogeneous group of many etiologies, with atherosclerotic or other mechanisms likely predominating over occult atrial fibrillation in the patients enrolled in these trials. The ARCADIA trial (NCT03192215) is testing apixaban versus aspirin in a subset of ESUS patients who have markers of atrial myopathy.

Section 6 Recommendations 2020
6.1 Acute Antiplatelet Therapy

i. All patients with acute ischemic stroke or TIA not already on an antiplatelet agent should be treated with at least 160 mg of acetylsalicylic acid immediately as a one-time loading dose after brain imaging has excluded intracranial hemorrhage [Evidence Level A].

ii. For patients with dysphagia, acetylsalicylic acid (80 mg daily) or clopidogrel (75 mg daily) may be administered by enteral tube or acetylsalicylic acid by rectal suppository (325 mg daily) [Evidence Level A]. *Note: acetylsalicylic acid should only be administered orally once dysphagia screening has been performed and indicates absence of potential dysphagia.*

iii. Antiplatelet therapy should be started as soon as possible after brain imaging has excluded hemorrhage, within 24 h of symptom onset (ideally within 12 h) [Evidence Level B].

iv. For patients receiving intravenous thrombolysis therapy, avoid antiplatelet therapy within the first 24 h; antiplatelet therapy could then be initiated after brain imaging has excluded secondary hemorrhage [Evidence Level B].

v. For TIA or minor ischemic stroke patients who are being discharged from the emergency department, antiplatelet therapy should be started prior to discharge [Evidence Level C].

6.2 Antiplatelet Therapy for Secondary Stroke Prevention

i. For patients with ischemic stroke or TIA, antiplatelet therapy is recommended for long-term secondary stroke prevention to reduce the risk of recurrent stroke and other vascular events unless there is an indication for anticoagulant therapy [Evidence Level A].

ii. Antiplatelet therapy should be started as soon as possible after brain imaging has excluded hemorrhage, within 24 h of symptom onset (ideally within 12 h) [Evidence Level B].

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iii. For long-term secondary stroke prevention, either acetylsalicylic acid (80–325 mg daily), or clopidogrel (75 mg daily), or combined acetylsalicylic acid and extended-release dipyridamole (25mg/200 mg BID), are all appropriate treatment options and selection depends on patient factors or clinical circumstances [Evidence Level A]

6.2.1 Short-Term Dual Antiplatelet Therapy for Secondary Stroke Prevention

iv. For patients with an acute high-risk TIA or minor ischemic stroke of non-cardioembolic origin (NIHSS 0–3), who are not at high bleeding risk, dual antiplatelet therapy is recommended with clopidogrel 75 mg daily plus acetylsalicylic acid 81 mg daily for a duration of 21 d after the event, followed by antiplatelet monotherapy thereafter (acetylsalicylic acid or clopidogrel alone) [Evidence Level A].

v. **(Revised for 2020)**: Dual antiplatelet therapy for longer than the first 21 d following a TIA or minor stroke **is not recommended** unless there is a specific indication (e.g., arterial stent; symptomatic intracranial artery stenosis), due to an increased risk of bleeding without clear benefit beyond 21 d [Evidence Level B]. Patients should be counseled that dual antiplatelet therapy with acetylsalicylic acid and clopidogrel should continue for only 21 d, followed by antiplatelet monotherapy to be continued indefinitely.

vi. A single loading dose of clopidogrel (either 300 mg (CHANCE trial) or 600 mg (POINT trial)) and acetylsalicylic acid (160–325 mg) should be administered at the start of treatment [Evidence Level A].

vii. **(New for 2020):** Another reasonable short-term dual antiplatelet treatment option is the combination of daily low-dose acetylsalicylic acid plus ticagrelor (180 mg loading dose, followed by 90 mg bid) for 30 d [Evidence Level B].

viii. **(New for 2020):** For patients with a recent stroke or TIA due to symptomatic intracranial atherosclerotic stenosis of 70%–99%, and a low estimated bleeding risk, the SAMMPRIS protocol should be considered, which includes dual antiplatelet therapy (acetylsalicylic acid and clopidogrel) for the first 3 months, typically followed by antiplatelet monotherapy thereafter, in addition to intensive lipid-lowering therapy with high-dose statin, blood pressure treatment, and structured lifestyle modification addressing smoking cessation, exercise and diet [Evidence Level B].

6.2.2 Specific Clinical Situations

ix. **(New for 2020):** For patients with an embolic stroke of undetermined source, and no known atrial fibrillation, anticoagulant therapy **is not currently recommended** over low-dose acetylsalicylic acid for secondary stroke prevention [Evidence Level A]. *Additional trials are ongoing to investigate this issue.*

Section 6.2 Clinical Considerations

1. For patients who experience a stroke while receiving one antiplatelet agent, stroke etiology should be reassessed and addressed, and all other vascular risk factors aggressively managed. Either continuing the current agent or switching to a different antiplatelet agent are reasonable options. At the present time, evidence is lacking to make more specific recommendations.
2. **(New for 2020):** Pharmacogenetic testing can identify patients with clopidogrel resistance, however, its clinical implications for stroke prevention treatment are unclear at this time.
3. **(New for 2020):** For carefully selected patients with coronary artery disease or peripheral vascular disease meeting the eligibility criteria of the **COMPASS trial**, including a low-estimated bleeding risk and no history of lacunar stroke or hemorrhagic stroke, the combination of rivaroxaban 2.5 mg BID plus daily low-dose acetylsalicylic acid is a reasonable treatment option. It should not be used within the first month after a stroke event.

Section 7: Anticoagulant Therapy for Atrial Fibrillation

Oral anticoagulant therapy is strongly recommended for secondary stroke prevention in patients with atrial fibrillation. Anticoagulation for AF has been associated with a 66% relative risk reduction of recurrent stroke, with an absolute risk reduction of 7.3%.[45] Direct oral anticoagulants (DOACs) are generally preferred over warfarin for most patients with non-valvular atrial fibrillation (non-valvular is now defined as atrial fibrillation without moderate–severe mitral stenosis or mechanical heart valves).[46] A recent trial supports the use of rivaroxaban over warfarin for patients with atrial fibrillation and a bioprosthetic mitral valve.[47]

Clinicians are reminded to avoid inappropriate underdosing of DOACs, a practice that is associated with increased stroke risk. For patients with atrial fibrillation and chronic stable coronary artery disease (or >1-year post-percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG]), the addition of an antiplatelet agent to chronic DOAC therapy is not recommended as it increases bleeding risk without providing additional benefit in reducing ischemic events (cardiac or cerebral). The Atrial Fibrillation and Ischemic Events With Rivaroxaban in Patients With Stable Coronary Artery Disease Study (AFIRE) trial showed that rivaroxaban alone was as effective as the combination of rivaroxaban and aspirin in this patient population, with a lower incidence of bleeding.[48]

Section 7 Recommendations
7.1 Detection of Atrial Fibrillation following Stroke

i. Patients with suspected ischemic stroke or TIA should have a 12-lead ECG to assess for atrial fibrillation,

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myocardial infarction, or structural heart disease (e.g., left ventricular hypertrophy) as potential causes or risk factors of stroke [Evidence Level B].

ii. For patients being investigated for an acute embolic ischemic stroke or TIA, ECG monitoring for 24 h or more is recommended as part of the initial stroke work-up to detect paroxysmal atrial fibrillation in patients who would be potential candidates for anticoagulant therapy [Evidence Level A].

iii. For patients being investigated for an embolic ischemic stroke or TIA of undetermined source *whose initial short-term ECG monitoring does not reveal atrial fibrillation* but a cardioembolic mechanism is suspected, prolonged ECG monitoring for at least 2 weeks is recommended to improve detection of paroxysmal atrial fibrillation in selected patients aged ≥55 years who are not already receiving anticoagulant therapy but would be potential anticoagulant candidates [Evidence Level A].

iv. **(New for 2020):** For patients aged >65 years with ischemic stroke or TIA, routine pulse palpation is recommended to screen for undiagnosed atrial fibrillation [Evidence Level C].

7.2 Secondary Stroke Prevention in Patients with Atrial Fibrillation

i. Patients with ischemic stroke or TIA and atrial fibrillation should receive oral anticoagulant therapy for secondary stroke prevention [Evidence Level A].
   a. **(New for 2020):** For patients with an ischemic stroke or TIA and atrial fibrillation, oral anticoagulant therapy is strongly recommended [Evidence Level A]. It is recommended over acetylsalicylic acid [Evidence Level A] and dual antiplatelet therapy [Evidence level B].
   b. For most patients requiring anticoagulants for non-valvular atrial fibrillation, a direct oral anticoagulant (DOAC) such as apixaban, dabigatran, edoxaban, or rivaroxaban should be prescribed in preference over warfarin [Evidence Level A].
   c. For patients already receiving warfarin with good International Normalized Ratio (INR) control (range 2.0–3.0, with time in therapeutic range (TTR) of >70%) and without adverse effects, continuing warfarin, rather than switching to a DOAC, is a reasonable anticoagulant option [Evidence Level B]. Patient preferences should be considered in decision-making [Evidence Level C].
   d. When selecting an oral anticoagulant, patient specific criteria should be considered [Evidence Level C].

ii. For patients with acute ischemic stroke and atrial fibrillation who are being started on warfarin, routine use of bridging with heparin is not recommended [Evidence Level B].
   a. Bridging with antiplatelet therapy (e.g., low-dose acetylsalicylic acid) is suggested until the patient is anticoagulated within therapeutic range [Evidence Level C].

iii. For patients with ischemic stroke or TIA and atrial fibrillation who are unable to take oral anticoagulant therapy (DOAC or warfarin), acetylsalicylic acid alone is recommended unless also contraindicated [Evidence Level A].
   a. For patients at high risk of bleeding, dual antiplatelet therapy is not recommended in preference to anticoagulation as the risks of bleeding are comparable, and dual antiplatelet therapy is less effective for stroke prevention [Evidence Level B].

iv. For ischemic stroke or TIA in patients with atrial fibrillation who cannot receive long-term oral anticoagulant therapy, a left atrial appendage occlusion procedure may be considered [Evidence Level B].

v. For patients with a mechanical heart valve, warfarin is recommended for stroke prevention with careful INR monitoring; direct oral anticoagulants (DOACs) are contraindicated [Evidence Level B]. *Note, patients with bioprosthetic heart valves do not routinely require long-term anticoagulation.*

vi. **(New for 2020):** For patients with atrial fibrillation who experience ischemic stroke or TIA in spite of anticoagulant therapy, we recommend the following: (1) identify and address medication non-adherence; (2) ensure correct DOAC dosing or warfarin INR control; (3) avoid DOACs drug–drug interactions; (4) investigate for and treat other potential stroke etiologies; and (5) promote general vascular risk factor modification [Evidence Level C].

Section 7.2 Clinical Considerations Revised for 2020

Timing of Initiation of Oral Anticoagulant Therapy following Acute Stroke:

1. The optimal timing to start anticoagulant therapy after an ischemic stroke has not yet been well defined by clinical trial evidence and should be based on individual benefit/risk assessment taking into account the clinical circumstances, stroke severity, infarct size, imaging appearances, risk of hemorrhagic transformation, age, comorbidities, and estimated stroke recurrence risk.
2. There is a lack of randomized evidence to guide specific timing. According to expert consensus, a general approach to the target timing of initiation of DOAC therapy post-stroke is as follows:
   a. For patients with a brief TIA and no visible infarct or hemorrhage on imaging, anticoagulation may be started within the first 24 h post-TIA.
   b. For patients with a minor clinical stroke/small non-hemorrhagic infarct on imaging, anticoagulation may be started 3 d post-stroke.
   c. For patients with a moderate clinical stroke/moderate-sized infarct on imaging (without hemorrhage on CT), anticoagulation may be started 6–7 d post-stroke.
   d. For patients with a severe clinical stroke/large-sized infarct on imaging (without hemorrhage on CT), anticoagulation may be started 12–14 d post-stroke.
3. If anticoagulation is delayed beyond 24 h, it is recommended to obtain repeat brain imaging for reassessment prior to initiation of anticoagulation to exclude the presence of asymptomatic hemorrhagic transformation of the index infarct.

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4. It is reasonable to delay the initiation of anticoagulation for more than 2 weeks post-stroke if in the judgement of the clinician the risk of intracranial bleeding is felt to be high, for example, for some patients with large infarcts and those with hemorrhagic transformation.

Stroke while on DOAC Therapy

1. **(New for 2020):** For patients with atrial fibrillation who experience ischemic stroke or TIA despite anticoagulant therapy, either continuing the current agent or switching to a different anticoagulant agent are reasonable options. At the present time, evidence is lacking to make more specific recommendations.
2. The routine addition of acetylsalicylic acid to chronic anticoagulant therapy is not recommended because of increased bleeding risk without clear evidence of benefit and potential for harm unless there is a specific medical indication.

7.3 Enhancing anticoagulant therapy effectiveness in practice and minimizing bleeding complications.

i. Medication adherence should be continually assessed and reinforced for patients on all oral anticoagulants at each follow-up visit [Evidence Level B].
   a. Patients who are prescribed a DOAC should be reassessed at intervals and educated regarding the short half-life of this class of drugs, the importance of daily medication adherence and the dangers of missed doses or prolonged interruptions of therapy [Evidence Level C].
   b. For patients with atrial fibrillation taking warfarin, careful dosing and consistent INR monitoring is recommended to minimize adverse events; warfarin efficacy is dependent on maintaining therapeutic INR control and declines significantly when the INR falls below 2.0 [Evidence Level A].
   c. Patients and family members should be provided education, resources, and ongoing monitoring regarding atrial fibrillation and adherence to enhance compliance and address potential barriers in a timely way to facilitate self-management [Evidence Level C].

ii. **(New for 2020):** For patients prescribed DOAC therapy, avoid inappropriate underdosing as it is associated with increased stroke risk [Evidence Level C].

iii. For patients prescribed DOACs, creatinine clearance should be routinely monitored at least once annually, and when there is a change in health status [Evidence Level C].
   a. Dose adjustments or a change in selected agent may be required based on changes in renal function if detected [Evidence Level C].
   b. More frequent monitoring of renal function (every 6 months or more frequently) may be considered for patients with renal impairment or a dehydrating illness for medication adjustment if required, particularly for patients receiving dabigatran [Evidence Level C].

iv. For patients taking chronic oral anticoagulant therapy for non-valvular atrial fibrillation, the addition of antiplatelet therapy is not recommended due to increased bleeding risk unless there is a specific medical indication for antiplatelet therapy (e.g., recent vascular stent; certain mechanical heart valves) [Evidence Level B].

v. **(New for 2020):** For patients with atrial fibrillation and chronic stable coronary artery disease (and >1-year post-PCI or CABG), the addition of an antiplatelet agent to DOAC therapy is not recommended as it increases bleeding risk without providing any significant benefit in reducing ischemic events (cardiac or cerebral) [Evidence Level B].

Section 8: Perioperative Management of Anticoagulant and Antiplatelet Therapy (New for 2020)

This edition features a new section on perioperative antithrombotic management – a commonly encountered issue in the stroke population and one in which practice variations abound. Our recommendations are aligned with Thrombosis Canada.[49] For stroke or TIA patients who require temporary interruption of chronic antiplatelet or anticoagulant therapy for an upcoming elective surgery, decisions regarding the duration of therapy interruption depend on the agent and the estimated bleeding risk associated with the surgery or procedure. The goal is to minimize the risk of ischemic stroke while simultaneously minimizing the risk of clinically important (major) bleeding. Patients should avoid unnecessary or prolonged interruptions of their antithrombotic therapy. Clinicians should communicate clear instructions to patients regarding their perioperative management plan before an elective procedure.

Because DOACs have a rapid offset (average half-life of approximately 12 h) and a rapid onset of action, the duration of DOAC interruption can be kept short to minimize the risk of ischemic stroke. This approach of standardized DOAC interruption and resumption appeared safe in the Perioperative Anticoagulation Use for Surgery Evaluation (PAUSE) study of 3007 DOAC-treated patients; the 30-d post-operative rates of arterial thromboembolism and major bleeding were <1% and <2%, respectively.[50] For patients undergoing a minimal-bleed-risk procedure, anticoagulants can generally be continued without interruption, with some caveats; for DOACs, it is reasonable to omit the morning DOAC dose before the procedure to reduce bleeding risk.

Descriptions of type of surgery or procedure and bleeding risk category:

- A **high-bleed-risk surgery or procedure** includes major abdominal surgery (e.g., cancer resection), major thoracic surgery, major orthopedic surgery, and any cardiac, spinal, or intracranial surgery. Any patient having neuraxial anesthesia is classified as high-bleed-risk because of the risk for spinal epidural hematomas which could cause limb paralysis.
- A **low-to-moderate-bleed-risk surgery or procedure** includes most surgeries that are <1-h duration and procedures that do not involve neuraxial anesthesia.
- A **minimal-bleed-risk surgery or procedure** includes tooth extractions, root canal, skin biopsies, cataract surgery, and selected colonoscopies, for which anticoagulants can be

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continued without interruption. Permanent pacemaker and internal cardiac defibrillator implantation, as well as cardiac catheterization, also can be done without stopping anticoagulants.

Section 8 Recommendations 2020

i. Patients with atrial fibrillation or a mechanical heart valve who are receiving oral anticoagulant therapy and require a procedure associated with a **minimal risk of bleeding** (e.g., tooth extraction, skin biopsy, cataract removal, cardiac pacemaker) should not have anticoagulation interrupted around the time of the procedure [Evidence Level B].

ii. For patients with atrial fibrillation receiving a DOAC for stroke prevention who require temporary DOAC interruption for an elective surgery or procedure, the following approach is recommended [Evidence Level B]:
   a. For a **low-to-moderate-bleed-risk** surgery or procedure, stop the DOAC the day before the procedure and the day of the procedure (i.e., skip 2 d total), and restart the day after the procedure.
   b. For a **high-bleed-risk** surgery or procedure, stop the DOAC 2 d before the procedure, the day of the procedure, and one day after the procedure (i.e., skip 4 d total).

   Note: An exception involves patients on dabigatran with impaired renal function (CrCl <50 mL/min) in whom an additional 1–2 d of interruption is suggested before surgery or procedure. Refer to clinical considerations for additional information.

iii. For patients with atrial fibrillation receiving **warfarin** for stroke prevention who require temporary warfarin interruption for an elective surgery or procedure:
   a. For patients at **low-to-moderate stroke risk** (e.g., CHADS2 score 0–4), warfarin should be stopped for 5 d pre-procedure, and resumed within 24 h post-procedure, without heparin bridging [Evidence Level A].
   b. For patients at **high-stroke risk** (e.g., CHADS2 score 5–6 or prior perioperative stroke), heparin bridging is suggested during warfarin interruption, typically with twice-daily subcutaneous injections of low-molecular-weight heparin for 3 d before and 3 d after the surgery or procedure [Evidence Level B]. If bridging is used pre-operatively, it is recommended to forego post-operative bridging in selected patients, especially those undergoing high-bleed-risk procedures [Evidence Level B].

iv. For patients with a **mechanical heart valve** who are receiving warfarin for stroke prevention and require temporary warfarin interruption for elective surgery or procedure, stopping warfarin 5 d pre-procedure is recommended and should be resumed within 24 h post-procedure [Evidence Level A].
   - Heparin bridging is recommended for selected patients with a mitral valve prosthesis and for high-risk patients with an aortic valve prosthesis (e.g., with additional risk factors for stroke) [Evidence Level B].
   - If bridging is used pre-operatively, it is recommended to forego post-operative bridging in selected patients, especially those undergoing high-bleed-risk procedures [Evidence Level B].

v. For patients receiving **acetylsalicylic acid** for stroke prevention who require an elective or urgent (within 7 d) carotid endarterectomy (CEA) or coronary artery bypass surgery, acetylsalicylic acid should be continued without interruption [Evidence Level B].

vi. For patients who are receiving **dual antiplatelet therapy** with acetylsalicylic acid and a P2Y12 inhibitor (e.g., clopidogrel, ticagrelor) for secondary stroke prevention who require urgent CEA (within 7 d), acetylsalicylic acid and a P2Y12 inhibitor should be continued perioperatively [Evidence Level C].

vii. For patients undergoing other types of surgery, continuing **acetylsalicylic acid** could be considered before a low/moderate-bleed-risk surgery or procedure. Interrupting **acetylsalicylic acid** before a high-bleed-risk surgery or procedure could be considered for 7–10 d [Evidence Level C].

Section 8 Clinical Considerations
Perioperative management of patients undergoing a minimal-bleed-risk procedure

1. For patients undergoing minor procedures that are considered minimal-bleed-risk (refer to definition above), it is not routinely necessary to stop anticoagulants. However, there are some caveats to the management of such patients:
   a. Any of the minimal-bleed-risk procedures could be considered as having a higher bleed risk warranting anticoagulant interruption (e.g., tooth extraction in a patient with poor dentition or cataract surgery with retrobulbar anesthesia) based on individual patient circumstances.
   b. In patients receiving a DOAC who are undergoing a minimal bleed-risk procedure, it is prudent to omit the morning DOAC dose just before the procedure because the peak anticoagulant effect, occurring 1–3 h after intake, may coincide with the timing of the procedure and may increase the risk for bleeding.
   c. For pacemaker or ICD implantation, patients can continue warfarin, but the INR should be <3.0 at the time of the procedure.
   d. For coronary angiography, continuing anticoagulants if a femoral artery approach is used may not be advisable as such patients are at increased risk for developing a hematoma or false aneurysm.
   e. For colonoscopy, anticoagulation can be continued in selected patients in which the likelihood of polypectomy or multiple biopsies is low.

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f. For dental procedures, oral tranexamic acid mouthwash can be used before and 2–3 times daily after the procedure to reduce bleeding since such oral bleeding, although not clinically important, may cause distress to patients.

Perioperative management of patients undergoing a moderate-to-high-risk procedure

1. Patients having a **high-bleed-risk** surgery or procedure only need to be off DOACs for 2 d before the procedure, corresponding to a 60–68-h interval between the last DOAC dose and the time of surgery, which means there is little to no residual anticoagulant effect at surgery given the 12–15-h half-life of DOACs.
2. Patients having a **low/moderate-bleed-risk** surgery or procedure only need to be off DOACs for 1 d before the procedure, corresponding to a 36–42-h interval between the last dose and the surgery.
3. For all patients, no DOAC should be taken on the day of surgery/procedure.
4. The exception to this approach is patients on dabigatran with impaired renal function (creatinine clearance <50 mL/minute). Because dabigatran is cleared primarily by the kidneys, a longer interruption interval is needed (4 d before a high-bleed-risk surgery: 2 d before a low/moderate-bleed-risk surgery).
5. Post-operative resumption of DOACs should wait at least 24 h after a low/moderate-bleed-risk surgery or procedure and 48–72 h after a high-bleed-risk surgery or procedure.
6. There are caveats to post-operative DOAC management: First, the 48–72-h resumption interval can be extended if there is greater than expected post-operative bleeding, which is important because the full anticoagulant effect of DOAC is almost immediate after oral intake. Second, in patients who are unable to take medications by mouth and who are at high risk for venous thromboembolism, low-dose low molecular weight heparin (LMWH) can be given for the initial 1–3 post-operative days

Section 9: Management of Extracranial Carotid Disease and Intracranial Atherosclerosis

Carotid endarterectomy (CEA) has been shown to prevent stroke recurrence in patients who have sustained a minor stroke or TIA with ipsilateral high-grade carotid stenosis. For those with 50%–99% stenosis, the number of persons needed to undergo surgery to prevent one ipsilateral stroke in five years was estimated to be 9 for men versus 36 for women. Women with symptomatic disease had significantly higher odds of 30-d mortality following CEA compared with men. (adjusted OR = 1.4, 95% CI 1.02–1.94).[51]

The use of CEA for asymptomatic carotid artery disease is controversial. One-year results from the recent SPACE-2 trial,[52] indicated there were no significant differences between groups (CEA vs. best medical management) in the occurrences of any stroke after day 30, up to one-year, ipsilateral stroke, disabling stroke, any death, myocardial infarction, restenosis or TIA. The trial was terminated early due to low recruitment. In this same trial, there were no significant differences in the same outcomes for the comparison of best medical management versus carotid-artery angioplasty.

Section 9 Recommendations 2020
9.1 Symptomatic Carotid Artery Stenosis

9.1.1 Imaging

i. If revascularization is being considered for carotid stenosis based only on carotid ultrasound, then CTA or contrast enhanced MRA is recommended to confirm the degree of stenosis and guide surgical decision-making, as well as to assess for tandem disease [Evidence Level C].
   a. Conversely, carotid ultrasound may be required after initial diagnosis of carotid stenosis using CTA or contrast-enhanced MRA if heavily calcified plaque or other features make quantification of stenosis less reliable [Evidence Level C].

9.1.2 Indications for carotid revascularization

i. Patients with a symptomatic event attributed to an ipsilateral **50%–99%** carotid artery stenosis should be evaluated without delay for potential carotid revascularization by a health professional with stroke expertise [Evidence Level B].
   a. In men with **50%–99%** and women with **70%–99%** symptomatic carotid artery stenosis, CEA is recommended and should be performed as soon as possible following the qualifying event [Evidence Level A].
   b. In women with **50 to 69** percent symptomatic carotid stenosis, CEA may be considered in those at highest risk of stroke recurrence and upon consideration of other patient factors [Evidence Level B].

9.1.3 Procedures

i. Carotid revascularization (CEA or Carotid artery stenting [CAS]) should be performed by a proceduralist/centre that routinely audits their performance results, especially perioperative stroke, and death rates [Evidence Level B].
   a. For CEA, the randomized trials upon which these recommendations are based (benefits accrued for patients undergoing surgery within 6 months of symptoms) involved combined perioperative stroke and death rates of 6%–7% [Evidence Level A].
   b. For CAS, the randomized trial upon which these recommendations are based involved combined peri-procedural stroke and death rates of 5% [Evidence Level B].
ii. CEA is generally more appropriate than CAS for patients over age 70 years who are otherwise fit for surgery as current evidence indicates stenting carries a higher peri-procedural risk of stroke and death in older patients [Evidence Level A].

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iii. Carotid stenting may be considered for patients who are not operative candidates for technical, anatomic, or medical reasons [Evidence Level A].

9.1.4 Timing

i. In clinically stable patients (men and women), CEA should be performed as early as possible following a qualifying event [Evidence Level B] and ideally within 14 d [Evidence Level A].
ii. In **men with 50%–69%** stenosis, the benefit of CEA is greatest when performed within 14 d of the qualifying event [Evidence Level A] and is attenuated when performed beyond 14 d of the qualifying event *(Refer to Appendix Three below for summary of recurrent stroke risk at various time points).*

Section 9.1 Clinical Considerations

1. Most data regarding optimal timing of carotid revascularization for symptomatic carotid stenosis are derived from studies of CEA and not CAS. However, it may be reasonable to consider that similar recommendations regarding timing also apply to CAS.
2. In exceptional situations, if local system barriers preclude timely access to CEA while CAS is more rapidly accessible, this latter revascularization procedure may be considered in patients otherwise considered eligible for CAS. However, every effort must be made to enable local systems of care to ensure timely access to CEA.
3. It may be reasonable to consider delaying CEA beyond 48 h of the qualifying event as surgery before this time may be associated with a higher risk of perioperative complications, particularly when the qualifying event was a stroke and not a TIA.
4. For patients with moderate or severe stroke due to symptomatic carotid stenosis, the benefit of carotid revascularization is uncertain and should be considered on an individual basis, as such patients were excluded from trials of CEA and CAS.
5. In acute stroke patients with tandem lesions (cervical carotid stenosis or occlusion and ipsilateral intracranial large vessel occlusion) who have undergone endovascular thrombectomy (EVT) but in whom no acute CAS has been performed during the EVT procedure, subsequent carotid revascularization by CAS and CEA should be considered if the patient otherwise remains a candidate for either procedure (as determined by residual degree of carotid stenosis, stroke severity, patient recovery, infarct size, reperfusion and bleeding risk, and other factors).

9.2 Asymptomatic and Remotely Symptomatic Carotid Artery Stenosis

i. Individuals with asymptomatic carotid artery stenosis should receive aggressive medical management of risk factors as defined throughout the *Secondary Prevention of Stroke* Module (e.g., blood pressure, diabetes, cholesterol, antiplatelet therapy, smoking cessation, and lifestyle changes) [Evidence Level B].
ii. CEA may be considered for **highly selected patients with 60%–99%** carotid stenosis who are asymptomatic or were remotely symptomatic (i.e., greater than six months prior to presentation) [Evidence Level A].
    a. The benefit of CEA for **women with 60%–99%** asymptomatic carotid artery stenosis is not clear and should only be considered in highly selected patients [Evidence Level B] in consultation with a health professional with stroke expertise.
    b. Patients should be evaluated to determine eligibility for CEA, such as a life expectancy of more than five years, and an acceptable risk of surgical complications [Evidence Level A].
    c. In carefully selected patients, CEA should be performed by a surgeon who routinely audits their performance results and demonstrates a less than 3% risk of peri-operative morbidity and mortality [Evidence Level B].
    d. Important improvements in best medical therapy (control of blood pressure, lipids, diabetes, and smoking) since the major trials of endarterectomy for asymptomatic stenosis possibly make their results less applicable to contemporary management practise (Evidence Level C).
iii. Carotid stenting may be considered in patients with **60%–99% asymptomatic** carotid stenosis who are not operative candidates for technical, anatomic, or medical reasons provided there is a less than 3% risk of periprocedural morbidity and mortality [Evidence Level A].

Section 9.2 Clinical Considerations:

1. Although their impact on clinical decision-making regarding revascularization of asymptomatic patients is uncertain, several factors may confer a higher risk of stroke in patients with asymptomatic stenosis, including:
    a. Progression of stenosis over time.
    b. Ipsilateral covert brain infarcts on imaging.
    c. Ipsilateral intracranial embolization detected on transcranial Doppler.
    d. Plaque morphology on non-invasive imaging (e.g., volume, echolucency, intraplaque hemorrhage).

9.3 Symptomatic Vertebral Artery Stenosis

i. **(New for 2020):** For patients with symptomatic vertebral artery stenosis (extracranial or intracranial), medical therapy is recommended over stenting for secondary stroke prevention [Evidence Level B].

9.4 Symptomatic Intracranial Artery Stenosis

i. For patients with a recent ischemic stroke or TIA due to symptomatic **intracranial artery stenosis of 70%–99%**, medical therapy is recommended over stenting for secondary stroke prevention [Evidence Level B].

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Note: The SAMMPRIS protocol consisted of 3 months of dual antiplatelet therapy with acetylsalicylic acid and clopidogrel (excluding high-bleeding risk patients), and is typically followed by antiplatelet monotherapy thereafter, plus intensive lipid-lowering therapy with high-dose statin, blood pressure treatment, and structured lifestyle modification addressing smoking cessation, exercise, and diet.

ii. In patients who have been managed with maximal medical therapy in the presence of intracranial stenosis and experience a recurrent stroke, there is lack of evidence to guide management decisions; intracranial angioplasty (with or without stenting) may be reasonable in carefully selected patients [Evidence Level C].

9.5 Cervicocephalic Artery Dissection

i. **(New for 2020):** For patients with ischemic stroke or TIA that is preceded by head/neck trauma, cervical spine mechanical trigger event, or prominent head/neck pain, a diagnosis of carotid or vertebral artery dissection should be suspected [Evidence Level C].

ii. For patients with ischemic stroke or TIA in whom a carotid or vertebral artery dissection is suspected, CTA or MRA of the head and neck (or catheter angiogram) is recommended as the diagnostic neurovascular imaging test rather than ultrasound [Evidence Level C].
Note: CTA or MRA are the preferred non-invasive diagnostic imaging tests for patients with a suspected cervicocephalic artery dissection, as neck ultrasound does not fully visualize the vertebral arteries and can miss distal carotid artery dissections originating above the angle of the jaw.

iii. Antithrombotic therapy for stroke prevention is recommended for individuals with a diagnosis of an acute or recent extracranial carotid or vertebral artery dissection [Evidence Level B].
   a. **(New for 2020):** There is an uncertainty about the comparative efficacy of antiplatelet therapy versus anticoagulation with heparin or warfarin; either treatment is considered reasonable based on current evidence [Evidence Level B]; decisions should be based on individual risk/benefit analysis taking into consideration the imaging features of the dissection (presence and degree of stenosis, intraluminal thrombus, vessel occlusion, pseudoaneurysm), brain imaging, patient characteristics, and estimated bleeding risk [Evidence Level C].
   b. The optimal duration of antithrombotic therapy post-dissection is uncertain; decisions may be based on individual clinical factors and imaging appearances on follow-up vascular imaging [Evidence Level C].

iv. There is a lack of evidence regarding the safety and efficacy of anticoagulation for intracranial arterial dissections and treatment decisions should be individualized [Evidence Level C].

Section 9.5 Clinical Considerations

1. There is an insufficient evidence at this time to make a recommendation regarding the use of DOACs in patients with arterial dissections [Evidence Level C].

Section 10: Other Cardiac Issues in Individuals with Stroke

Since the last edition, a new randomized trial[53] and additional meta-analyses and other reports further support PFO closure for secondary stroke prevention in selected patients.[54–56] Given that TIA can be difficult to differentiate from mimics and the fact that only one of the PFO trials enrolled patients with TIA as an index event, clinicians should be cautious when contemplating PFO closure for TIA unless there is a high certainty of ischemia; accordingly, these 2021 recommendations no longer indicate TIA as an unqualified indication for closure. There is now moderate-strength evidence that PFO closure may be targeted to patient groups with higher risk echocardiographic features.

For patients with heart failure and without atrial fibrillation, the COMMANDER-HF trial,[57] which compared rivaroxaban to standard care, found no significant difference in the frequency of the primary outcome (a composite of death from any cause, MI, or stroke) between groups. The risks of the individual components of the primary outcome did not differ between groups with the exception of the risk of stroke, which was reduced significantly with rivaroxaban (1.08 vs. 1.63 events/100-person years; HR = 0.66, 95% CI 0.47–0.95). In the Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial,[58] which compared the effectiveness of anticoagulation compared with antiplatelet therapy for stroke prevention in patients with heart failure in sinus rhythm, warfarin was associated with a significantly reduced risk of ischemic stroke (HR = 0.52, 95% CI 0.33–0.82, $p = 0.005$); however, the risks of major and minor hemorrhages were significantly increased.[59]

Section 10 Recommendations
10.1 Patent Foramen Ovale (PFO)

i. Patients with a recent ischemic stroke suspected to be related to a PFO should have an evaluation by healthcare professionals with stroke and cardiovascular expertise [Evidence Level C].

ii. For carefully selected patients with a recent ischemic stroke attributed to a PFO, PFO device closure plus long-term antiplatelet therapy is recommended over long-term antithrombotic therapy alone **provided all** the following criteria are met [Evidence Level A]:
   a. Age 18–60 years.
   b. The diagnosis of the index stroke event is confirmed by imaging as a non-lacunar embolic ischemic stroke.
   c. The patient has been evaluated by a neurologist or healthcare professional with stroke expertise, and the PFO is felt to be the most likely cause for the index

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stroke event following a thorough etiological evaluation that has excluded alternate likely etiologies.

iii. **(New for 2020):** It is reasonable to recommend against 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) [Evidence Level B].

iv. For patients requiring long-term anticoagulation for other reasons, the benefit of PFO closure is uncertain, and treatment decisions should be based on individual patient characteristics and risk versus benefit profile [Evidence Level C].

v. For patients with a recent ischemic stroke attributed to a PFO who do not undergo PFO closure and are aged 60 years or younger, either antiplatelet or anticoagulant therapy is recommended for secondary stroke prevention, unless there is a separate evidence-based indication for chronic anticoagulant therapy [Evidence Level B].

Section 10.1 Clinical Considerations

1. Warfarin can reduce recurrent stroke; however, this benefit may be outweighed by the increased risk of major hemorrhage.
2. The role of DOACs is unknown in this population.

10.2 Aortic Arch Atheroma:

i. Aortic arch atheroma should be managed according to the stroke prevention recommendations included in all relevant sections of the *Secondary Prevention of Stroke Module* [Evidence Level C].

ii. In the Aortic Arch Related Cerebral Hazard (ARCH) trial, no significant difference was found in individuals treated with dual antiplatelet therapy (acetylsalicylic acid plus clopidogrel) as compared with warfarin; the effectiveness of anticoagulant therapy compared with antiplatelet therapy in this context is uncertain and the choice should be individualized [Evidence Level B].

10.3 Heart Failure, Decreased Left Ventricular Ejection Fraction, Cardiac Thrombus

i. For patients with ischemic stroke or TIA who are in sinus rhythm and have a left atrial or left ventricular thrombus demonstrated by echocardiography or other imaging modality, anticoagulant therapy is recommended for greater than 3 months [Evidence Level C].

ii. For patients with ischemic stroke or TIA who are in sinus rhythm and have severe left ventricular dysfunction (ejection fraction ≤35%) without evidence of left atrial or left ventricular thrombus, the net benefit of anticoagulant therapy (with either vitamin K antagonists or DOACs) compared with antiplatelet therapy is uncertain, and the choice of management strategies should be individualized [Evidence Level B].

Section 11: Cancer-Associated Ischemic Stroke

A diagnosis of cancer can increase the risk of stroke in the months or years following the diagnosis, particularly among persons with lung cancer or with more advanced cancers.[60,61] Thrombosis is a common complication of malignancy and represents a frequent cause of death in cancer patients with a history of stroke.

Section 11 Recommendations
11.1 Cancer-Associated Ischemic Stroke

i. Patients with active malignancy who experience an arterial ischemic stroke or TIA should undergo a standard etiological work-up for their stroke, including vascular imaging and cardiac rhythm monitoring [Evidence Level C]. *Refer to Section 1 on Stroke Investigations for additional information.*

ii. Stroke mechanisms associated with malignancy may be considered when determining etiological investigations, including non-bacterial (marantic) endocarditis, hypercoagulability, paradoxical embolism due to venous thrombosis, tumor-related vascular compression, and stroke related to anti-cancer treatments [Evidence Level C].

iii. In patients with active malignancy and arterial ischemic stroke or TIA in whom a cancer-associated hypercoagulable state may have contributed to the stroke, anticoagulation could be considered over antiplatelet therapy [Evidence Level C].
   a. When anticoagulation is used, low-molecular weight heparin therapy is preferred [Evidence Level C]. The role of DOACs is unknown but under study and may be reasonable after consideration of patient preference.

Section 11 Clinical considerations

1. Management decisions for these patients should be made in collaboration with a health professional with expertise in Hematology, Oncology or Thrombosis, and should take into account the type of underlying cancer, the risk of bleeding, the extent of neoplastic disease, the patient's overall prognosis and expressed goals of care.
2. In patients with active malignancy and arterial ischemic stroke or TIA with a concurrent venous thromboembolism (deep vein thrombosis [DVT] or pulmonary embolism [PE]) in whom the stroke is presumed to be due to a paradoxical embolus, anticoagulation for secondary prevention should follow guidelines for the management of DVT and PE in cancer patients which includes LMWH and selected DOACs (Refer to www.thrombosiscanada.ca).

Challenges and Future Directions

Advances in stroke prevention, driven by high-quality clinical studies, continue to inform each new edition of these guidelines.

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However, we are still far from adequately addressing, at a global level, the 10 modifiable risk factors that account for 90% of the population attributable risk of stroke.[62] The largest impact on stroke prevention globally will likely be achieved by continued large-scale efforts to address hypertension, diabetes, diet, exercise, smoking, in addition to atrial fibrillation at both policy and individual levels.

A key tenet of secondary stroke prevention remains the importance of identifying the most likely stroke etiology and tailoring therapy accordingly. Although the completed ESUS trials found no overall benefit of anticoagulation, further research aims to identify whether specific subgroups may benefit. Dual pathway inhibition is a promising strategy.[63] Newer anticoagulants targeting factor XI represent promising future treatments for stroke prevention. Studies are ongoing (NCT02604667) and others are needed to better define when and how occult cancer should be investigated in cryptogenic stroke patients, and if found, what antithrombotic regimen best protects these patients from recurrent arterial strokes.[64]

Immediate challenges to optimal secondary stroke prevention would therefore include the need to develop, grow, and maintain systems for virtual delivery of care to patients through telemedicine.[65,66] The SARS-CoV2 virus represents a well-documented challenge to acute stroke care[67] but its impact on the risk of stroke recurrence, either directly among patients having been infected with the virus, or on other patients who have suffered collateral damage from diminished access to stroke care, will be important to now study.

A challenge that concerns research in all fields of medicine – including stroke[68] – is the need to ensure adequate sex and gender representation in therapeutic trials to ensure generalizability of results to both men and women. This edition is the first of our guidelines to start incorporating a sex and gender descriptive analysis into the literature review for each recommendation, and future editions will strive to include gender and sex-based recommendations where appropriate.

Summary

The 2020 update of the *Canadian Stroke Best Practice Secondary Prevention of Stroke Recommendations* provide a common set of guiding principles for important aspects of secondary stroke prevention, emphasizing that individuals who have experienced a stroke or TIA require access expert prevention care in a timely way. In Canada, coordinated systems have evolved over time, growing the number of stroke prevention services and protocols to increase access in many under-serviced areas. In the age of Covid-19, there are new opportunities to provide prevention interventions remotely to narrow the inequities in access to care.

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David J Gladstone (First author) and Alexandre Y. Poppe (Senior Author) are co-chairs of the *Secondary Prevention of Stroke* expert writing group and lead authors contributing to all aspects of the development, evidence and data analysis, writing, editing, and final approval of this manuscript; M. Patrice Lindsay is corresponding author, senior editor of the Canadian Stroke Best Practice Recommendations (CSBPR) and of this manuscript, involved in all aspects of scientific literature review, writing group deliberations, external review process, manuscript preparation, and a writer of supplementary documentation. Aline Bourgoin, Jafna

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Supplementary Material

To view supplementary material for this article, please visit https://doi.org/10.1017/cjn.2021.127.

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