Canadian Stroke Best Practices

CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

Secondary Prevention of Stroke

Seventh Edition, Update 2020

SECONDARY PREVENTION of STROKE Scientific Writing Group: David J. Gladstone (Co-Chair), Alexandre Y. Poppe (Co-Chair), James Douketis, William Semchuk, Aline Bourgoin, Jafna Cox, John B. Falconer, Brett R. Graham, Marilyn Labrie, Lena McDonald, Jennifer Mandzia, Daniel Ngui, Paul Pageau, Amanda Rodgerson, Tammy Tebbutt, Carmen Tuchak, Jacob A Udell, Stephen van Gaal, Karina Villaluna, Dar Dowlatshahi, Shelagh Coutts, Theodore Wein, Manraj K.S. Heran, Pascale Lavoie, Rebecca McGuff, and M. Patrice Lindsay; on Behalf of the Canadian Stroke Best Practice Recommendations Advisory Committee, in collaboration with the Canadian Stroke Consortium.

Canadian Stroke Best Practice Recommendations

Secondary Prevention of Stroke ~ Seventh Edition Update 2020

Table of Contents

Section One: INTRODUCTION and OVERVIEW

Introduction

Introduction to the Canadian Stroke Best Practice Recommendations

The Canadian Stroke Best Practice Recommendations (CSBPR) are intended to provide up-to-date evidence-based guidelines for the prevention and management of stroke, and to promote optimal recovery and reintegration for people who have experienced stroke (patients, families, and informal caregivers). The CSBPR are under the leadership of the Heart and Stroke Foundation, Canada (HSF).

The theme of the Seventh Edition of the CSBPR is **Building connections to optimize individual outcomes**. People who have experienced a stroke often present to the healthcare system with multiple comorbid conditions – some that may contribute to their stroke, some that are consequences of their stroke, and some unrelated. One study revealed that approximately 80% of people who survive a stroke have on average five other conditions and a wide range of psychosocial issues (Nelson et al, 2016). These conditions must be considered as treatment and ongoing care planning is personalized and person-centred. In addition, there is strong evidence of the intrinsic connections between the heart and brain, and management of people following stroke should take heart health and possible association with vascular cognitive impairment into consideration. The healthcare system is often designed in siloes with different planning and organization for individual conditions, that are not integrated across conditions, even related vascular conditions. As people transition across settings and phases of care following a stroke, they report experiencing anxiety and feeling quite overwhelmed. Individualized care and ensuring connections are made within the community have a significant impact on patient short and long-term outcomes.

The Seventh Edition of the CSBPR includes a broader wholistic focus and take into consideration issues of multimorbidity and increasing complexity of people who experience stroke. This is particularly relevant for this module on the ***secondary prevention of stroke***, where people who have experienced a stroke often already have several other comorbidities present. In addition, a more purposeful review of sex and gender representation in the seminal clinical trials upon which the recommendations are based has been undertaken to determine the extent to which available evidence has included both male and female subjects in sufficient proportions to be able to detect outcomes and generalize to a broader population. These findings are presented in the discussion sections of the module and integrated into the actual recommendations where appropriate to do so. Accompanying performance measures have been expanded to include system indicators, clinical indicators and new patient reported outcome measures, supporting our wholistic focus.

The goal of disseminating and implementing these recommendations is to optimize evidence-based stroke care across Canada, reduce practice variations in the care of stroke patients, and narrow the gap between current knowledge and clinical practice.

These recommendations have been developed in collaboration with the Canadian Stroke Consortium. We work closely with the Canadian Cardiovascular Society, Thrombosis Canada and Hypertension Canada to ensure alignment of recommendations across guidelines where possible and appropriate.

Profile of Stroke Care in Canada:

- The global lifetime risk of stroke in 2016 was 24.7% for men and 25.1% for women. (GBD2016)
- Every year, more than 62,000 people with stroke and transient ischemic attack are treated in Canadian hospitals. Moreover, it is estimated that for each symptomatic stroke, there are approximately nine covert strokes that result in subtle changes in cognitive function and processes.

- Ischemic stroke and transient ischemic attack account for approximately 85 - 90% of all stroke cases presenting to hospitals in Canada. In-hospital mortality from ischemic stroke is lower compared to hemorrhagic stroke (15% versus 40%) (H&S, based on CIHI2019 DAD data analysis).
- Stroke and other cerebrovascular diseases are the third leading cause of death in Canada and the second leading cause of death globally. While the number of deaths from stroke is decreasing in North America and parts of Europe, it is increasing in most other countries.
- Stroke is a leading cause of adult disability, with more than 400,000 people in Canada living with the effects of stroke.
- The annual cost of stroke is approximately $3.6 billion, considering both healthcare costs and lost economic output.
- The combined Canadian healthcare system costs and out-of-pocket caregiver costs for dementia amounted to $10.4 billion in 2016. By 2031, this figure is expected to increase to $16.6 billion [a]
- The human cost of stroke is immeasurable.

Secondary Prevention of Stroke Update 2020 Module Overview and Definitions

Scope of the Secondary Prevention of Stroke Module:

This Secondary Prevention of Stroke module focuses on management of recurrent stroke risk reduction in patients who have experienced an initial stroke or transient ischemic attack. In some cases, this module will also guide healthcare providers with guidance for individuals at high risk of a stroke or transient ischemic attack based on current health status and the significant presence of one or more vascular risk factors.

Primary prevention and the reduction of risk factor prevalence in the general population are not the main focus of the *Canadian Stroke Best Practice Recommendations*; therefore, only selected recommendations related to primary prevention are included. A comprehensive set of recommendations for primary prevention are available in existing high quality guidelines developed by other organizations (such as Canadian Cardiovascular Society, Hypertension Canada Blood Pressure guidelines, Canadian Task Force on Preventative Health Care, and the Canadian Physical Activity Guidelines).

Primary prevention

Primary prevention can be a population-based approach to prevent disease among communities or an individually based clinical approach to disease prevention, directed toward preventing the initial occurrence of a disorder in otherwise healthy individuals. Primary prevention can be implemented in the primary care setting, and the physician, nurse practitioner, team nurses, physician assistant, pharmacist or patient may initiate a discussion of heart conditions, stroke, and vascular cognitive impairment risk reduction. It can also be implemented at a population level using legislative, regulatory, and public awareness interventions.

Primary prevention and health promotion recommendations related to heart conditions, stroke, transient ischemic attack, vascular cognitive impairment, and peripheral vascular disease emphasize the importance of screening and monitoring and treating those patients at high risk of a first clinical event. Primary prevention areas of focus include lifestyle (healthy diet, physical activity, being tobacco-free,

[a] Public Health Agency of Canada. Mapping connections: an understanding of neurological conditions in Canada: the National Population Health Study of Neurological Conditions. Ottawa (ON): Public Health Agency of Canada; [modified 2014 Dec 09; cited July 30, 2015]. bhttp://www.phac-aspc.gc.ca/publicat/cd-mc/mc-ec/index-eng.php.

stress reduction and limiting alcohol, recreational drugs), and screening and management of medical risk factors such as hypertension, dyslipidemia, diabetes, and atrial fibrillation.

Implementation of primary prevention strategies ideally would involve a Shared Decision-Making conversation between the patient and the provider to ensure the patient's goals are incorporated into therapy decisions.

Primary prevention also includes the development of strategies to improve population health such as policies that create environments that facilitate making healthy choices the easier choices (examples include smoke-free legislation, revised Canada's Food Guide as well as policies that support active and public transportation). These strategies are often led by health-oriented organizations and agencies such as Heart & Stroke, Canadian Cardiovascular Society, Canadian Lung Association, Canadian Cancer Society, Thrombosis Canada, Hypertension Canada, Diabetes Canada, Alzheimer Society of Canada, Health Canada, and national and provincial public health agencies and services.

Secondary prevention:

Secondary prevention is an individually based clinical approach aimed at reducing the risk of a recurrent vascular event in individuals who have already experienced a stroke, angina, transient ischemic attack, myocardial infarction, heart failure, heart rhythm abnormalities, structural heart disease, vascular cognitive impairment or peripheral vascular disease.

Secondary prevention recommendations are directed to those risk factors shown to reduce recurrent and prolong survival after vascular conditions, including attention to lifestyle (prudent diet, reduced sodium intake, increased level of activity, maintaining ideal body weight, smoking cessation, and controlling alcohol intake), and management of medical conditions such as hypertension, dyslipidemia, and heart rhythm management (e.g., atrial fibrillation). Secondary prevention recommendations can be addressed in a variety of settings—acute care, vascular prevention clinics (generalized or specific to conditions such as stroke, heart failure, post myocardial infarction), and community-based care settings. They pertain to patients initially seen in primary care, those who are treated in an emergency department and then released and those who are hospitalized and receive treatment in hospital because of angina, myocardial infarction, heart failure, heart rhythm abnormalities, structural heart disease, stroke, transient ischemic attack, vascular cognitive impairment or peripheral vascular disease.

Recommendations for secondary prevention of vascular conditions should be implemented throughout the recovery phase, including during inpatient and outpatient rehabilitation, reintegration into the community and ongoing follow-up by primary care practitioners. Secondary prevention should be addressed at all appropriate healthcare encounters on an ongoing basis following angina, myocardial infarction, heart failure, heart rhythm abnormalities, structural heart disease, stroke, transient ischemic attack, vascular cognitive impairment, or peripheral vascular disease.

Definitions:

Transient ischemic attack (transient ischemic attack):

Transient ischemic attack (often called a 'mini-stroke') is a clinical diagnosis that refers to a brief episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, with clinical symptoms, and without imaging evidence of infarction (Easton, 2009; Sacco et al, 2013). Transient ischemic attack and minor acute ischemic stroke fall along a continuum. Transient ischemic attack symptoms fully resolve within 24 hours (usually within one hour). If any symptoms persist beyond 24 hours, then this would be considered a stroke, not a transient ischemic attack. A transient ischemic attack event is significant as it can be a warning of a future stroke event. Patients and healthcare professionals should respond to an acute transient ischemic attack as a potential emergency.

Transient ischemic attack and minor acute ischemic stroke follow along a continuum that cannot be differentiated by symptom duration alone.

Minor Stroke:

A minor ischemic stroke (also sometimes referred to as mild, or non-disabling stroke) refers to a brain infarct that is typically small and associated with a mild severity of clinical deficits or disability and may not require hospitalization.

Note: For practical purposes, individuals presenting with symptoms of transient ischemic attack or minor stroke should all follow similar assessment, diagnosis and management processes as described throughout this module. Differentiation between transient ischemic attack and minor stroke is less relevant, and all management should be informed by clinical history, presentation, and diagnostic imaging. Current evidence has shown that at least 20% of individuals presenting with transient ischemic attack will experience a subsequent more involved stroke, emphasizing the need for aggressive secondary prevention for this group (NEJM 2016).

Ischemic Stroke

An ischemic stroke is an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal cell death attributable to ischemia (blockage of an artery or vein), based on pathological, imaging, or other objective (clinical) evidence of cerebral, spinal cord, or retinal focal ischemic injury based on symptoms persisting ≥24 hours or until death, or until other etiologies have been excluded (Sacco et al 2013).

Cerebral Venous Sinus Thrombosis Stroke (CVST)

A cerebral venous sinus thrombosis stroke is an infarction or hemorrhage in the brain, spinal cord, or retina because if thrombosis of a cerebral venous structure. Symptoms or signs caused by reversable edema without infarction or hemorrhage do not qualify as stroke (Sacco et al 2013).

Cryptogenic Stroke:

Cryptogenic stroke is defined as a brain infarction not clearly attributable to a definite cardioembolism, large artery atherosclerosis, small artery disease or other identifiable cause despite extensive investigation (Saver et al 2017). This group accounts for 25 to 40% of all stroke (Saver, 2016; Yaghi et al, 2017).

Embolic Stroke of Undetermined Source (ESUS) *Embolic stroke of undetermined source* describes a subset of cryptogenic strokes that represent approximately 9 – 25% of ischemic strokes, that meet the following criteria (Tsivgoulis et al, 2017; Ntaios, JACC 2020 [17%]):

- 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
- No other likely cause of stroke (e.g., dissection, arteritis, cancer)

Notable Updates in CSBPR Secondary Prevention of Stroke 2020

The 2020 update of the Canadian Stroke Best Practice Recommendations Secondary Prevention of Stroke module reinforces the growing and changing body of research evidence available to guide stroke prevention services. A coordinated and organized approach to assessment and ***aggressive risk factor management is emphasized throughout this module.***

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.

Highlights of significant updates and new additions to the Secondary Prevention of Stroke best practice recommendations for 2020 that are based on new and emerging evidence include:

- New simplified triage recommendations for patients with acute transient ischemic attack and minor strokes
- Updated recommendations regarding the diagnostic workup of patients with ischemic stroke or transient ischemic attack (imaging, echocardiography for PFO detection, pulse palpation for opportunistic atrial fibrillation screening, and thrombophilia testing)
- New section on perioperative management of anticoagulant and antiplatelet therapy
- New recommendation regarding the ESUS treatment trials (embolic strokes of undetermined source)
- Updated recommendation regarding the duration of dual antiplatelet therapy after transient ischemic attack or minor stroke
- New recommendation regarding the THALES trial treatment regimen
- New recommendation regarding permissive hypertension in patients experiencing hemodynamic ischemia related to critical stenosis of an extracranial or intracranial artery.
- New recommendation regarding vertebral artery stenting
- Updated recommendations regarding management of patients with atrial fibrillation
- Updated recommendations regarding management of patients with patent foramen ovale
- Update recommendations regarding cervicocephalic artery dissection.
- New recommendation on PCSK9 inhibitor therapy for lipid management
- New recommendation regarding patients with cancer-associated stroke
- New recommendation regarding influenza vaccination and cautions related to air pollution.
- Recommendations on virtual care for delivery of secondary stroke prevention

In addition, there are emerging trends in stroke prevention research that have been reviewed and discussed by the writing group. These are areas that the group felt were important to monitor but the evidence is not sufficiently clear enough at the time of publication of these guidelines to make specific recommendation statements. These areas include genetic prediSPoSition and biomarkers (e.g., ACE2), and Transcranial Doppler.

Guideline Development Methodology

The *CSBPR* present high-quality, evidence-based stroke care guidelines in a standardized framework to support healthcare professionals across all disciplines. Implementation of these recommendations are expected to reduce practice variations and close the gaps between evidence and practice.

The recommendations are targeted to health professionals throughout the health system who care for those affected by stroke. Health system policy makers, planners, funders, senior managers, and administrators who are responsible for the coordination and delivery of stroke services within a province or region will also find this document relevant and applicable to their work.

The methodology for updating the recommendations includes 14 distinct steps to ensure a thorough and rigorous process. These include the following (details available online):

1. Establish an expert interprofessional writing group representing relevant disciplines across the continuum of care and range of settings (Appendix One).
2. Establish Community Consultation and Review Panel comprised of people with lived experience, including people with stroke, caregivers, and family members.
3. Systematic search, appraisal and update of research literature up to May 2020.
4. Systematic search and appraisal of external reference guideline recommendations.
5. Create and or update of evidence summary tables.
6. Writing group review and revision of existing recommendations, development of new recommendations as required, adhering to all elements defined within the Agree 2 criteria where appropriate (Agree Trust)
7. Writing group review and revision of existing recommendations, development of new recommendations as required, then final voting to achieve consensus.
8. Submission and internal review of proposed module update by the Canadian Stroke Best Practice and Quality Advisory Committee.
9. External review by leading experts in Canada and internationally, and final edits as required (Appendix One).
10. Update of educational materials and implementation resources.
11. Final approvals, endorsement and translation of chapter.
12. Publication, public release, and dissemination of final module update.
13. Continue with ongoing review and update process.

The detailed methodology and explanations for each of these steps in the development and dissemination of the *CSBPR is* available in the *Canadian Stroke Best Practice Recommendations Overview and Methodology* manual available on the Canadian stroke best practices website at https://www.strokebestpractices.ca/recommendations/overview-methods-and-knowledge-exchange.

Management of Conflicts of Interest within CSBPR: All potential participants in the recommendation development and review process are required to sign confidentiality agreements and to declare all actual and potential conflicts of interest in writing prior to participation. Any conflicts of interest that are declared are reviewed by the Chairs of the CSBPR Advisory Committee and appropriate Heart & Stroke staff members for their potential impact. Potential members of any writing group who have conflicts that are considered to be significant with respect to the topics within the module of interest are not selected for writing group or reviewer roles. Participants who have conflicts for one particular topic area are identified at the beginning of discussions for that topic and are recused from voting. If the persons in conflict are one of the cochairs then they are recused from chair responsibilities for that discussion, and another non-conflicted participant assumes the chair role for that discussion and voting to ensure balanced and unbiased discussions. Heart & Stroke senior staff members, who do not have any conflicts of interest, participate in all writing group discussions, and will intervene if there is any perceived untoward bias by a writing group member. Declarations of Conflict of interest for writing group members can be found in Appendix One.

Assigning Evidence Levels: The writing group was provided with comprehensive evidence tables that include summaries of all high-quality evidence identified through the literature searches. The writing group discusses and debates the value of the evidence and through consensus develops a final set of proposed recommendations. Through their discussions, additional research may be identified and added to the evidence tables if consensus on the value of the research is achieved. All recommendations are assigned a level of evidence ranging from A to C, according to the criteria

defined in Table 1. When developing and including "C-Level" recommendations, consensus is obtained among the writing group and validated through the internal and external review process. This level of evidence is used cautiously, and only when there is a lack of stronger evidence for topics considered important system drivers for stroke care (e.g., transport using ambulance services or some screening practices). An additional category for Clinical Considerations has been added for the Sixth Edition. Included in this section are expert opinion statements in response to reasonable requests from a range of healthcare professionals who seek guidance and direction from the experts on specific clinical issues faced on a regular basis in the absence of any evidence on that topic.

Table 1: Summary of Criteria for Levels of Evidence Reported in the *Canadian Best Practice Recommendations for Stroke Care* (Update 2020)

Level of Evidence	Criteria*
A	Evidence from a meta-analysis of randomized controlled trials or consistent findings from two or more randomized controlled trials. Desirable effects clearly outweigh undesirable effects or vice versa.
B	Evidence from a single randomized controlled trial or consistent findings from two or more well-designed non-randomized and/or non-controlled trials, and large observational studies. Meta-analysis of non-randomized and/or observational studies. Desirable effects outweigh or are closely balanced with undesirable effects or vice versa.
C	Writing group consensus on topics supported by limited research evidence. Desirable effects outweigh or are closely balanced with undesirable effects or vice versa, as determined by writing group consensus.
Clinical Consideration	Reasonable practical advice provided by consensus of the writing group on specific clinical issues that are common and/or controversial and lack research evidence to guide practice.

* (adapted from Guyatt et al. 2008) [12]

Acknowledgements

Heart &Stroke gratefully acknowledges the *Secondary Prevention of Stroke* writing group leaders and members all of whom have volunteered their time and expertise to the update of these recommendations. Members of the Canadian Stroke Consortium were involved in all aspects of the development of these recommendations. These recommendations underwent external review by: Jason Andrade, Rohit Bhatia, Margie Burns, Elena Adela Cora, Roxanne Cournoyer, Laurent Derex, Paul Dorian, Charles Duffy, Eric Ehrensperger, Yuriy Flomin, Kirsten George-Phillips, Sarah Grant, Milan Gupta, Rahul Jain, Shirin Jalani, Glen Jickling, Hooman Kamel, Hong Kao, Lisa Keon, Lisa Korec, Catherine Legault, Gerald MacDonald, GB John Mancini, Michael MacDonald, Kaylee Murphy, Kelvin Kuan Huei Ng, Darlene Peacock, Andre Roussin, Joanna D Schaafsma, Peter Senior, Aleksander Tkach, Sean Virani, and Janice Williams. We thank the Canadian Stroke Best Practices and Quality Advisory Committee members, including Eric Smith (Co-Chair), Anita Mountain (Co-Chair), Leanne Casaubon, Gord Gubitz, Dar Dowlatshahi, Dylan Blacquiere, Louise Clement, Thalia Field, Farrell Leibovitch, Christine Papoushek, Jeffrey Habert, Barbara Campbell, Joyce Fung, Michael Hill, Tim Hillier, Thomas Jeerakathil, Eddy Lang, Pascale Lavoie, Beth Linkewich, Colleen O'Connell, Melanie Penn, Jai Shankar, Debbie Timpson, Theodore Wein, and Katie White. We acknowledge and thank Norine Foley and the evidence analysis team at workHORSE; Laurie Charest of Heart & Stroke for her coordination of the CSBPR teams and processes; Andrea deJong, Francine Forget Marin and the Heart & Stroke internal teams who contributed to the development of these recommendations and publication: Communications, Translation, Knowledge Translation, Engagement, Health Policy and Digital

Solutions.

Community Consultation and Review Panel (CCRP) Members

Heart & Stroke is especially grateful to the members of the Community Consultation and Review Panel who reviewed all sections of this module, shared their personal experiences and insights on what did or would have made their journey optimal. The members of the Secondary Prevention of Stroke CCRP included: Cheryl Beattie, Jennifer Bogart, Dan Dobbin, Glen Hilton, Judy Hilton, Allan Morrison and additional volunteers who provided input.

Funding

The development of the *CSBPR is* funded in its entirety by Heart & Stroke. No funds for the development of these guidelines come from commercial interests, including pharmaceutical and device companies. All members of the recommendation writing groups, and external reviewers are volunteers and do not receive any remuneration for participation in guideline development, updates, and reviews. All participants complete a conflict of interest declaration prior to participation.

Citing the Prevention of Stroke 2020 Module

SECONDARY PREVENTION of STROKE Scientific Writing Group: David J. Gladstone (Chair), Alexandre Y. Poppe (Co-Chair), Aline Bourgoin, Jafna Cox, James Douketis, John B. Falconer, Brett R. Graham, Marilyn Labrie, Lena McDonald, Jennifer Mandzia, Daniel Ngui, Paul Pageau, Amanda Rodgerson, William Semchuk, Tammy Tebbutt, Carmen Tuchak, Jacob A Udell, Stephen van Gaal, Karina Villaluna , M. Patrice Lindsay, Dar Dowlatshahi, Shelagh Coutts, and Theodore Wein; on Behalf of the Canadian Stroke Best Practice Recommendations Advisory Committee, in collaboration with the Canadian Stroke Consortium. Secondary Prevention of Stroke Module*, 7th Edition, 2020*. In M. Patrice Lindsay, Anita Mountain, Gord Gubitz, Dariush Dowlatshahi, Leanne K Casaubon, Rebecca McGuff and Eric E Smith (Editors), on behalf of the Canadian Stroke Best Practices and Quality Advisory Committee in collaboration with the Canadian Stroke Consortium and the Canadian Partnership for Stroke Recovery. Canadian Stroke Best Practice Recommendations Seventh Edition, 2020; Toronto, Ontario Canada: Heart and Stroke Foundation.

The recommendations included in this module are also published in the Canadian Journal of Neurological Science.

Gladstone, D., Lindsay, M., Douketis, J., Smith, E., Dowlatshahi, D., Wein, T., . . . Poppe, A. (2021). Canadian Stroke Best Practice Recommendations: Secondary Prevention of Stroke Update 2020. Canadian Journal of Neurological Sciences / Journal Canadien Des Sciences Neurologiques, 1-69. doi:10.1017/cjn.2021.127

English link: https://www.cambridge.org/core/journals/canadian-journal-of-neurological-sciences/article/canadian-stroke-best-practice-recommendations-secondary-prevention-of-stroke-update-2020/A73EB82EEB054DD001AD5A19627F0D83
French link: https://www.cambridge.org/core/journals/canadian-journal-of-neurological-sciences/article/canadian-stroke-best-practice-recommendations-secondary-prevention-of-stroke-update-2020/A73EB82EEB054DD001AD5A19627F0D83

Comments

We invite comments, suggestions, and inquiries on the development and application of the *Canadian Stroke Best Practice Recommendations.* Please forward comments to the Heart and Stroke Foundation's Stroke Team at strokebestpractices@heartandstroke.ca.

Section Two: Core Elements of Delivery of Secondary Stroke Prevention Services

A critical component of secondary stroke prevention is access to specialized stroke prevention services (SPS), ideally provided by dedicated stroke prevention clinics. Stroke prevention clinics (or similar vascular prevention clinics, services or models of care) provide a comprehensive interdisciplinary approach to prevention of first or recurrent stroke, conduct detailed assessments by a range of healthcare disciplines, facilitate timely access to appropriate diagnostic testing and interventions, and provide education to patients and families. They also promote continuity of care between acute care facilities, rehabilitation services, the patient, their family and caregivers, primary care providers, and other community care service providers.

In 2016, the Heart and Stroke Foundation conducted a Stroke Prevention Services Resource Inventory (SPSRI) through which 123 stroke prevention services were identified across Canada. Services were available in every province; however, there were considerable differences between prevention services with respect to structural elements such as models of care, hours of operation, SPS team members, and availability of diagnostic services; process elements such as wait times for appointments and wait times to access services such as imaging and Holter monitoring; and outcome elements such as monitoring quality of care and stroke recurrence rates.

The SPSRI inventory was created using a modified Delphi methodology. The foundation of the SPSRI is the Canadian Stroke Best Practice Recommendations, and in particular this module on the Secondary Prevention of Stroke. A review of the literature was performed to identify different models of prevention services, and core elements of such services. Consultations were then held with stroke prevention service providers, funders, and policy makers. An extensive list of elements of prevention services was then developed that aligned with the evidence-based best practice recommendations. The draft SPSRI underwent three rounds of voting by a wide range of stroke care clinicians, managers, patients, and funders to identify the final set of elements for the inventory. SPSRI was sent to a specific contact person at each of the 123 identified SPS. A total of 119 services completed the inventory (97% response rate). Analysis of the responses informed further refinement of the inventory and final inclusion list of core elements of stroke prevention services.

A framework of key components of delivering prevention services (Figure Two), and a comprehensive list of the core elements of stroke prevention services (Table Two). The purpose of this framework and list of elements is multifaceted, and are to:

- enable stroke prevention service providers, regardless of size or location, to assess the types and level of services provided.
- identify gaps in the core elements of prevention services to inform planning, development, and quality improvement initiatives.
- identify issues of access to stroke prevention services, based on location of services as well as hours of operation (e.g., once a week versus daily), and availability of healthcare professionals and diagnostic services (e.g., CAT scanner) onsite.
- to identify the list of elements present and not yet available that serve as enablers to implementation of the stroke best practice recommendations included in this update of the Secondary Prevention of Stroke Best Practices update 2020.
- to strengthen service provision and increase accountability.

FIGURE TWO:
CSBPR CORE ELEMENTS OF STROKE PREVENTION SERVICES UNDERLYING FRAMEWORK
(© HEART & STROKE)

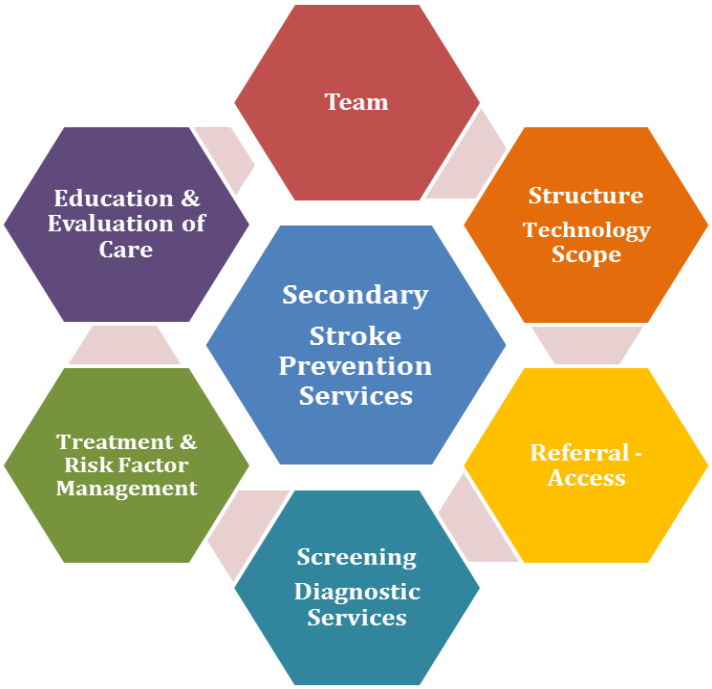

TABLE TWO: H&S CSBPR Core Elements of Stroke Prevention Services (Update 2020)

Secondary Prevention Services (SPS) Core Element	Alignment with CSPBR* Sections	Description ^
Organizational Elements of Stroke Prevention Services		
Designated Prevention Services	CSBPR-SPOS Section 1, 3	❑ The SPS is identified and acknowledged within the local/regional health system as providing stroke prevention services. ❑ The SPS is conducted in a specific space within a hospital or the community, such as within the ambulatory/outpatient clinics or a physician's office, or through virtual modalities. ❑ The SPS follows protocols and pathways for an individualized evidence-based prevention strategy for patients. ❑ Emergency departments have responsibility to provide SPS to patients or ensure referrals are made to an appropriate SPS prior to patient discharge from the ED. ❑ The timing of initial assessment in the SPS is based on current recommended time frames based on time from symptom onset and presentation. Access to the SPS will be expedited based on risk stratification. ❑ The SPS are accessible to stroke and transient ischemic attack patients with disabilities (e.g., physical, cognitive, and perceptual). ❑ The SPS make provisions to provide care to and support patients with aphasia and other communication challenges.

Operation Times		❑ The SPS has set hours of operation that are communicated to all referral sources.
Stroke Team Staffing	SPOS Section 1	❑ The SPS has access to an interprofessional group of stroke experts, including neurology, internal medicine, vascular surgery, neurosurgery, rehabilitation medicine, neuropsychiatry, nursing, pharmacy, psychology, neuropsychology, rehabilitation therapy (such as physiotherapy, occupational therapy, speech-language pathology), social work, dietetics, community liaisons/navigator, research, and administration. ❑ Additional Experts are accessed directly within the SPS or through timely pre-arranged referral patterns outside the SPS. ❑ Staff have appropriate training and education to remain current with updates to the CSBPR. ❑ Staff are able to provide care to persons with aphasia and other communication challenges (such as having skills in supportive conversation).
Service Scope	SPOS Section 1	❑ The SPS has a clearly defined scope of practice that is communicated to referring sources – states the range and types of services offered, such as same day urgent referrals, or less urgent services only. ❑ The SPS defines its role as providing at minimum a one-time assessment; or additionally assessment and short-term follow-up, long-term follow-up, and/or collaborative care with primary care practitioner.
Referral Mechanisms	SPOS Section 1 Acute Stroke Management, Sections 1, 3	❑ The SPS has a standardized referral process and documentation (e.g., referral form) to access services. ❑ The SPS has a designated person coordinating referrals and scheduling appointments appropriate to degree of urgency. ❑ The SPS is aware of, and in communication with all potential referral sources regarding referral process and target response times. ❑ All referring sources are aware of the referral process and required documentation for access to the SPS. ❑ The SPS has processes to regularly review and prioritize referrals and respond appropriately based on degree of urgency. ❑ The SPS monitors wait times from referral to first assessment appointment. ❑ The SPS provides access to patients living outside the immediate catchment for the service, to support patients living in rural and remote settings.
Use of Technology – Virtual Care	Virtual Care Section 1	❑ The prevention service considers virtual care technology to increase access to services for all patients, especially those living in rural and remote settings without local access to stroke specialists and those who do not require in-person visits. ❑ The SPS established/validated criteria to determine the best modality for each patient and each encounter based on the purpose and goals for each visit, and taking into account patient values, preferences, and health needs. ❑ 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.
Access to Diagnostic Services	SPOS Section 1, 7, 8, 10, 11, 12	❑ The SPS has timely access to relevant diagnostic services onsite (brain and vascular imaging with CT scan/MRI, CTA, carotid ultrasound, ECG, Holter monitoring, prolonged cardiac monitoring, echocardiogram, laboratory services).

	ASM Sections 1, 3	❑ Agreements are in place with diagnostic departments to access services on a more urgent basis when required (e.g., same day, 24-hour, one week). ❑ If services are not available on site, agreements are in place for timely access to diagnostic services within the region, or next closest facility providing such services without undue wait times.
Care Delivery Elements of Stroke Prevention Services		
Screening and Assessment	SPoS; ASM; MCF	❑ SPS routinely screens patient for vascular risk factors in accordance with current evidence-based stroke guidelines. ❑ The SPS has a defined set of validated screening practices that includes timing of such screens in accordance with best available evidence. ❑ Lifestyle risk factors to be assessed include smoking, lifestyle behaviours, diet, weight, exercise, sodium, alcohol consumption, birth control and hormone replacement therapy, recreational drug use, and medication adherence. ❑ Screening for medical risk factors include blood pressure, depression, cognition, atrial fibrillation, bleeding risk, lipids, diabetes, and other underlying cardiac issues. ❑ Assessment for sequelae of stroke, including stroke severity, physical functioning, swallowing, fatigue, depression, cognition, and post-stroke neuropathic pain as appropriate. H&S Post-Stroke Checklist available to support screening of patients. ❑ Protocols in place for use of validated tools to support assessment and diagnosis. ❑ Process in place to refer patients to other specialists as required to determine or confirm presence of risk factors (such as cardiology for atrial fibrillation determination).
Diagnosis and Etiology	SPoS; ASM; MCF	❑ Diagnosis should specify the type of stroke or transient ischemic attack the patient has experienced (i.e., ischemic, or hemorrhagic, and if latter whether subarachnoid or intracranial hemorrhage). ❑ Underlying etiology should be determined with appropriate investigations when possible and communicated to care providers and patient.
Treatment	SPoS sections 3-12	❑ Develop individualized stroke prevention plan for each patient, including defining agreed upon goals of care. ❑ Initiate treatment strategies for identified risk factors and clinical conditions as specified in the CSBPR. ❑ Process in place for timely access to carotid revascularization services onsite or through referral to closest centre providing services, within CSBPR target treatment times (as soon as possible, within 2 weeks of index stroke or transient ischemic attack event). ❑ SPS has processes in place to access rehabilitation (inpatient or community) to meet needs of patients.
Follow-up Practices	SPoS all sections ToCFS Rehab	❑ On follow-up, SPS routinely monitors patients for achievement of therapeutic targets and stability within targets. ❑ On follow-up, SPS routinely monitors patients for adherence to prescribed risk factor management strategies and therapies. ❑ SPS re-assesses patients for ongoing physical, functional, psychological, and social changes. ❑ SPS has process in place for patients and primary care providers to re-access SPS services for a patient if changes in

		health status, or additional consultation on prevention management is required. ❑ SPS has process in place for patients who do not have a primary care provider, to assist with identification of a primary care provider, or continuing to follow patient as required within the SPS. ❑ The SPS staff have processes in place to review each patient's driving status (e.g., driver/non-driver, holds drivers' license) and follow National guidelines and reporting requirements when indicated.
Communication and Continuity		❑ Must have timely method of communication of recommendations to the referring physicians, the patient's primary care provider, and other members of the patient's circle of care to ensure continuity of care. ❑ Communications should address and include information on completed assessments and findings, diagnosis, etiology, treatment plan, prescribed/recommended therapies, additional referrals, and clarification on who is responsible for ongoing follow-up, prescription renewals, and long-term management as well as referral back to SPS if needed.
Patient and Family Elements of Stroke Prevention Services		
Education, Promotion of Self-Management	ToCFS Sections 1, 2 SPoS Section 7	❑ SPS routinely provides personalized verbal education to patients and families, and caregivers. ❑ The SPS provides written and electronic educational resources (such as HSF Your Stroke Journey). ❑ The SPS assesses patient, family and caregiver knowledge, self-management capability, and learning needs for skills and coping mechanisms (e.g., using HSF Post-Stroke Checklist). ❑ Education materials are available in a range of formats, are culturally appropriate for the catchment population, aphasia friendly, and other languages as required. ❑ Translation services available for patients during SPS visits if required.
Linkages	ToCFS Section 6	❑ Provide patients and families with links to community resources and programs to support stroke recovery and implementation of prevention strategies, such as smoking cessation programs, community dietitians, community-based exercise programs, diabetic education programs, stroke support groups. ❑ The SPoS is able to initiate appropriate referrals for home care support services, specialized equipment, and process for driving assessment as required. ❑ The SPoS is able to recommend and or refer patients to community resources and programs to support adherence to prescribed risk factor management strategies and therapies (including pharmacotherapies) thereby supporting stroke recovery.
Outcome and Quality Elements of Stroke Prevention Services		
Quality and Accountability	All modules	❑ The SPS has mechanisms in place to routinely collect data on patients, including time intervals from referral to follow-up, services provided, effectiveness/outcome of care, physical measurements (e.g., weight, blood pressure); and can capture changes over time. ❑ The SPS has a process for reporting data to staff, funders, and patients.

		❑ The SPS compares performance to pre-set targets and benchmarks and engages in quality improvement initiatives to achieve targets and readjust as appropriate. ❑ The SPS should engage in relevant clinical research in the area of stroke prevention when possible.

^ Based on literature review, Delphi-process feedback, Canadian Stroke Best Practice Recommendations, and Accreditation Canada Stroke Distinction Standards. * SPoS – Secondary Prevention of Stroke Best Practice module; ASM – Acute Stroke Management guidelines module; MCF – Mood, Cognition and Fatigue CSBPR module; ToCFS – Transitions of Care Following Stroke module; Rehab – Stroke Rehabilitation module

Canadian Stroke Best Practice Recommendations 2020
SECONDARY PREVENTION OF STROKE

PART Three: Secondary Prevention of Stroke Recommendations

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

Section One Recommendations 2020

NOTES on this recommendation

- *These recommendations (Section 1) pertain to the initial management of patients with a suspected acute transient ischemic attack or acute ischemic stroke who are not candidates for acute thrombolysis or endovascular thrombectomy. For patients with suspected acute stroke that warrants hyperacute assessment to determine eligibility for thrombolysis/endovascular thrombectomy, refer to the current CSBPR Acute Stroke Management recommendations.*
- Individuals experiencing acute stroke symptoms/signs should immediately go to an emergency department, ideally by calling 9-1-1 and transport by emergency medical services to rapidly initiate pre-hospital pathways.
- In reality, however, some people experiencing acute stroke symptoms/signs may present to an outpatient setting such as a primary care physician or family health team office, community clinic, or urgent care centre.
- Individuals experiencing symptoms/signs of acute stroke require rapid assessment, diagnosis, and determination of risk for a recurrent stroke. Patients diagnosed with a transient ischemic attack or minor ischemic stroke who are not candidates for hyperacute treatment with intravenous thrombolysis or endovascular thrombectomy may then be prioritized for secondary prevention of stroke assessment and management.
- Ischemic stroke is a heterogenous condition with many different subtypes and causes, and it is beyond the scope of this guideline to address all of them. This section focuses on the diagnostic studies that are relevant to the identification of common conditions (e.g., atherosclerosis, atrial fibrillation) or some uncommon conditions requiring immediate treatment (e.g., bacterial endocarditis).

1.0 Patients with acute stroke or transient ischemic attack 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 Hours)

i. Individuals presenting within 48 hours of symptoms consistent with a new acute stroke or transient ischemic attack 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 on-site 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 hours from the onset of an acute stroke or transient ischemic attack event should receive a comprehensive clinical evaluation and investigations as soon as possible by a healthcare professional with stroke expertise [Evidence Level B]. *Refer to Section 2.2 for more information on investigations*

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)[b]; 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 hours) 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 transient ischemic attack clinics are available that have rapid access to diagnostic services, and they may be considered as appropriate referral options for transient ischemic attack 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 transient ischemic attack [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 and hence 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/ transient ischemic attack 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 based on availability and patient characteristics [Evidence Level C].

Section 1.2 Clinical Considerations:

i. 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 transient ischemic attack 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

[b] Kapoor et al, CJNS 2020

completed as soon as possible after the symptomatic event, ideally within 7 days of symptom onset. MRI is particularly useful in lower risk patients with transient symptoms in whom the presence of ischemia would change their management.

ii. Common scenarios where urgent brain MRI can be valuable include:

a. Normal CT head despite symptoms persisting > 24 hours (if 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 transient ischemic attack 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 Table 1A 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]. Refer to Diabetes Canada Guidelines for further information related to glucose testing.*

c. **(NEW FOR 2020):** If giant cell arteritis is suspected (e.g., retinal ischemia or headache), ESR and 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 (for example, 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

1.4 A Detection of Atrial Fibrillation

i. Patients with suspected ischemic stroke or transient ischemic attack 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 transient ischemic attack, ECG monitoring for 24 hours 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 transient ischemic attack 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]. *Refer to CSBPR Secondary Prevention of Stroke Module Section 7 for additional guidance in management of patients with*

stroke and atrial fibrillation, and the Canadian Cardiovascular Society current recommendations on atrial fibrillation.

iv. **(NEW FOR 2020):** For patients aged >65 years with ischemic stroke or transient ischemic attack, pulse palpation or heart auscultation or ECG rhythm strip is recommended to screen for undiagnosed atrial fibrillation [Evidence Level B].

1.4 B Echocardiography

i. Echocardiography should be considered for patients with an embolic ischemic stroke or transient ischemic attack 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 transient ischemic attack 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 rehabilitation therapy, and assistance with activities of daily living) [Evidence Level B]. *Refer to Rehabilitation Module for additional information.*

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]. *Refer to CSBPR Virtual Care Toolkit 2020 for additional information and guidance.*

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]. *Refer to Heart & Stroke Virtual Care Decision Framework for additional guidance and criteria.*

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:

i. 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.

ii. 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. *Refer to Heart & Stroke Virtual Care Decision Framework for additional guidance and criteria.*

iii. 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. *Refer to CSBPR Virtual Care Toolkit 2020 for additional information and guidance.*

iv. 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. *Refer to CSBPR Post Stroke Checklist for additional information and guidance.*

v. Validated approaches to virtual neurological exams should be followed.

vi. Barriers to access, equity and utilization should be considered and work-around solutions implemented.

vii. Ensure processes in place for booking follow-up tests, referrals and other consultations following a virtual care visit.

viii. Ensure appropriate documentation and communication to other team members who may also be involved in care remotely.

ix. 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 SPS.

x. 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.

xi. Data collection and quality improvement mechanisms should be in place to monitor efficiency, effectiveness and quality of virtual care encounters.

Rationale

*The goal of outpatient management of transient ischemic attack and non-disabling ischemic stroke is **rapid** assessment and management to reduce the risk of a recurrent, possibly more serious, event.*

There is clear evidence that transient ischemic attacks or minor strokes are unstable conditions that warn of high future risk of stroke, other vascular events, or death. The risk of recurrent stroke after a transient ischemic attack has been reported as 4.7 percent within 90 days (Shahjouei et al. 2020), and the risk is "front-loaded", with 3.8 percent of recurrent strokes occurring in the first two days following initial symptom onset. These improved rates from the previous 20 percent reinforces the importance and benefits of contemporary aggressive management of stroke and transient ischemic attack patients to prevent recurrent events. The seven-day risk of stroke following a transient ischemic attack can be as high as 36 percent in patients with multiple risk factors. Timely initiation of secondary prevention medical therapy and carotid endarterectomy has been shown to significantly reduce the risk of major stroke after an initial transient ischemic attack or non-disabling stroke. A study by the TIARegistry.Org group reported updated rates that were less than half that expected from historical cohorts and could be explained by better and faster implementation of secondary stroke prevention strategies in this cohort through rapid-access transient ischemic attack clinics (N Engl J Med 2016;374:1533-42). Canada has also seen these decreased (Kapoor et al 2020) with emphasis on the need to continue implementation of aggressive secondary prevention strategies to prevent these rates increasing again.

People with lived experience and their families have also expressed the importance for early access to assessment and diagnosis to prevent a recurrent event. They emphasize the need to receive timely education about signs and symptoms of stroke, and clear explanations about the risk for recurrent

stroke and the relevance of the time frames for those at different risk levels for recurrence events. The wait time from an initial transient ischemic attack to further investigations can be a stressful time and this should be considered in management planning. They also expressed concerns about potential biases that some women report, especially when presenting with a transient ischemic attack, or fluctuating symptoms.

System Implications

1. Education for the public and healthcare professionals (primary, acute and specialists) about the urgency of assessment and management of transient ischemic attack or non-disabling ischemic stroke is critical to reduce the risk of recurrent, potentially more serious events.
2. Systems should be in place for patients and families who require ongoing education and support related to prevention and management of stroke and its associated risk factors.
3. Education and training for healthcare professionals who work in primary, secondary, and tertiary care settings, to enable the management of patients with transient ischemic attack or non-disabling ischemic stroke in a timely manner. Education should also include content about the heart-brain connection and need to approach care holistically, considering all vascular risk factors.
4. Processes, protocols, and infrastructure in place to enable rapid access to diagnostic tests and expertise for patients with transient ischemic attack or minor stroke in community healthcare settings and acute healthcare facilities.
5. Well-established and accessible stroke prevention clinics, or broader vascular prevention programs available in all communities through traditional or technological means; and referral pathways and promotion of programs for healthcare practitioners to increase timely access. These resources should be listed, easily accessible to primary care physicians and healthcare providers, and updated annually.
6. Stroke systems of care should develop virtual care service models to improve the accessibility of secondary prevention services for patients in rural and remote locations, and for patients who have difficulty attending in person appointments.
7. New 2020 – Cost & time of travel can be a barrier to rural & remote residents accessing distant specialty services. Individual's often decline referrals or fail to attend appointments due to travel time, cost, & adverse weather conditions, especially in winter. Cross-border (inter-provincial & provincial-territorial) virtual care have many challenges with regulatory barriers in terms of how health professions are regulated.
8. Monitoring, assessment, and improvement of program regarding uptake, adherence, and quality of stroke prevention programs to ensure patients can access effective services. Consideration should be given to community and individual barriers as well as motivators and enablers.
9. New 2020 – Virtual Care: Governments and organizations should consider ways to ensure that barriers to access and utilization are addressed and mitigated.
10. For patients who need Holter monitoring as part of their stroke evaluation, home delivery of ambulatory ECG monitors may be an option in some regions to improve patient access to such tests.

Performance Measures

1. Proportion of acute stroke and transient ischemic attack patients who are discharged alive from an emergency department or an inpatient stay and then readmitted to hospital for any cause within 7 days of index acute stroke discharge (KQI).
2. Proportion of patients with transient ischemic attack or non-disabling stroke who are investigated and discharged from the emergency department who are referred to organized secondary stroke prevention services at discharge. (KQI)
3. Time from first encounter with medical care (primary care or emergency department) to assessment by a stroke expert (in clinic or other setting).

4. Proportion of patients with motor and speech TIAs who have CT head and CTA completed (or other vascular imaging) within 24 hours of presentation.
5. Time from first encounter with medical care to brain imaging (CT/MRI); vascular imaging (Doppler of cervical arteries, CTA, or MR angiography); and electrocardiogram.
6. ***Developmental KQI:*** *Proportion of HIGHEST risk* transient ischemic attack *and non-disabling stroke patients who are investigated and managed within 24 hours in the ED or referred to organized secondary stroke prevention services (KQI)*

Measurement Notes

- Data access and quality with respect to timing of first encounter and referral dates and times.
- Primary care data from physician billing. This should rely on International Classification of Diseases (ICD) codes and not on physician descriptions of diagnoses, as these may be less accurate.
- Measures from other prevention recommendations in this document are also applicable to this recommendation but are not repeated here.

Implementation Resources and Knowledge Transfer Tools

Health Care Provider Information

- CSBPR: Acute Stroke Management, Neurovascular Imaging https://www.strokebestpractices.ca/recommendations/acute-stroke-management
- CSBPR Acute Stroke Management Module: Screening and Assessment Tools for Acute Stroke Severity: https://www.heartandstroke.ca/-/media/1-stroke-best-practices/acute-stroke-management/appendix-three
- CSBPR Virtual Healthcare Toolkit https://www.heartandstroke.ca/-/media/1-stroke-best-practices/csbpr7-virtualcaretools-13may2020
- Heart & Stroke: Post-Stroke Checklist: https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/002-17_csbp_post_stroke_checklist_85x11_en_v1
- Heart & Stroke: FAST Signs of Stroke: https://www.heartandstroke.ca/stroke/signs-of-stroke/fast-signs-of-stroke-are-there-other-signs
- Heart & Stroke: 2020 CPR & EEC Guidelines: https://cpr.heartandstroke.ca/s/article/Guidelines?language=en_US
- Canadian Cardiovascular Society: 2020 CCS/CHRS Comprehensive Guidelines for the Management of Atrial Fibrillation. https://ccs.ca/guidelines-and-position-statement-library/
- Thrombosis Canada clinical guides: https://thrombosiscanada.ca/clinicalguides/
- Diabetes Canada Clinical Practice Guidelines: http://guidelines.diabetes.ca/
- Alzheimer's Association Guideline Index https://www.alz.org/professionals/health-systems-clinicians/guidelines_index_(1)
- Recommendations of the 5th Canadian Consensus Conference on the Diagnosis and Treatment of Dementia: https://alz-journals.onlinelibrary.wiley.com/doi/full/10.1002/alz.12105
- American College of Chest Physicians (ACCP), Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. https://journal.chestnet.org/GuidelineAntithrombotic
- American College of Chest Physicians (ACCP) Anticoagulation Guidelines: http://www.chestnet.org/Guidelines-and-Resources

- Stroke Engine: Canadian Neurological Scale: https://strokengine.ca/en/assessments/canadian-neurological-scale-cns/
- Virtual neurological exam examples:
  - Hussona, M.A., Maher, M., Chan, D., Micieli, J.A., Jain, J.D., Khosravani, H., Izenberg, A., Kassardjian, C.D., Mitchell, S.B. The Virtual Neurologic Exam: Instructional Videos and Guidance for the COVID-19 era. Canadian Journal of Neurological Sciences, 2020; 00, 1-6. doi:10.1017/cjn.2020.96; Supporting videos: https://www.nqil.ca/initiatives/virtual-neuro-exam
  - American Academy of Neurology: https://www.aan.com/tools-and-resources/practicing-neurologists-administrators/telemedicine-and-remote-care/#Education
- CorHealth COVID-19 Stroke Memo #5 - RECOMMENDATIONS FOR AN APPROACH TO RAMPING UP IN-PERSON SECONDARY STROKE PREVENTION CLINIC SERVICES IN ONTARIO: https://www.corhealthontario.ca/Memo5_SPC_Resumption_August-7-2020-final.pdf
- CorHealth: Secondary Stroke Prevention Resources:
  - Stroke Prevention Infographic for Primary Care Providers
  - Stroke Prevention Clinic Patient Summary

  https://www.corhealthontario.ca/resources-for-healthcare-planners-&-providers/stroke-general/piwp/secondary-prevention/resources
- Depression, Obstructive Sleep Apnea and Cognitive Impairment – DOC Screening Tool http://www.docscreen.ca/about.html

Patient Information

- Heart & Stroke: Signs of stroke: http://www.heartandstroke.ca/stroke/signs-of-stroke
- Heart & Stroke: FAST Signs of Stroke: https://www.heartandstroke.ca/stroke/signs-of-stroke/fast-signs-of-stroke-are-there-other-signs
- Heart & Stroke: Stroke information: http://www.heartandstroke.ca/stroke/what-is-stroke
- Heart & Stroke: Atrial Fibrillation information: http://www.heartandstroke.ca/heart/conditions/atrial-fibrillation
- Heart & Stroke: Your Stroke Journey: https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/en-your-stroke-journey-v21
- Heart & Stroke: Post-Stroke Checklist: https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/002-17_csbp_post_stroke_checklist_85x11_en_v1
- Heart & Stroke: Risk Factors for Heart Disease and Stroke: https://www.heartandstroke.ca/-/media/pdf-files/iavc/health-information-catalogue/en-are-you-at-risk
- Heart & Stroke: Taking charge of your stroke recovery: 2020 Virtual healthcare checklist infographic: https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/csbp-infographic-virtual-healthcare-checklist
- Heart & Stroke: Canadian Resuscitation and First Aid Guidelines: https://cpr.heartandstroke.ca/s?language=en_US
- Heart & Stroke: Online and Peer Support

https://www.heartandstroke.ca/heart-disease/recovery-and-support/the-power-of-community

- Canadian Partnership for Stroke Recovery – Video Resources
  https://canadianstroke.ca/en/tools-resources/videos
- Stroke Engine: http://strokengine.ca/
- Canadian Mental Health Association: Bounce Back

  https://bounceback.cmha.ca/

Summary of the Evidence 2020

Patients who present with TIA or minor stroke are at increased risk of recurrent stroke, particularly within the first week following the initial event. A systematic review conducted by Giles & Rothwell (2007) pooled the results from 18 studies, consisting of 10,126 patients with TIA. The risk of stroke at days 2 and 7 was 3.1% 5.2%, respectively. Perry et al. (2014) examined stroke risk in 3,906 patients with TIAs admitted to 8 emergency departments over a 5-year period. In this cohort, 86 patients (2.2%) developed subsequent stroke within 7 days, and 132 (3.4%) at 90 days. Purroy et al. (2012) reported similar frequency of recurrent stroke among 1,137 patients admitted to 30 centers in Spain, presenting with TIA. Recurrent events occurred in 2.6% of patients within 7 days and 3.9% within 90 days. Following the first 30 days, the risk of recurrent stroke appears to decline. Mohan et al. (2011) included the results from 13 studies of patients recovering from first-ever stroke who were participants of hospital and community-based stroke registries. The cumulative risks of stroke recurrence were 3.1% at 30 days; 11.1% at one year; 26.4% at 5 years; and 39.2% at 10 years. Callaly et al. (2016) followed 567 participants of the North Dublin Population Stroke Study. The reported cumulative incidence of stroke recurrence was 5.4% at 90 days, 8.5% at one year and 10.8% at 2 years with a 2-year case fatality of 38.6%. These findings highlight the value of assessing patients who present with suspected stroke or TIA according to time since onset of symptoms.

Rapid clinical assessment by stroke specialists and subsequent investigations to differentiate TIA and minor stroke from other potential causes are essential to ensure that secondary prevention strategies can be implemented as soon as possible. Urgent TIA clinics provide such a model of care. The TIAregistry.org project is a prospective registry designed to follow patients presenting with TIA or minor stroke over a 5-year period. Patients were included if the event had occurred within the previous 7 days. The preliminary one-year results, which included 4,583 patients recruited from 61 sites in 21 countries from 1997-2003, indicated that 78.4% of patients were seen by a stroke specialist within 24 hours of the event (Amarenco et al. 2016). Most patients received key urgent investigations before discharge and appropriate treatments were initiated. For example, 5.0% of patients received a new diagnosis of atrial fibrillation, of which 66.8% received anticoagulant therapy before discharge. Carotid stenosis of ≥50% was found in 15.5% of patients, of which 26.9% underwent carotid revascularization before discharge. The one-year estimate of risk of the primary outcome, a composite of death from cardiovascular causes, nonfatal stroke and nonfatal acute coronary syndrome, was 6.2% (95% CI 5.5-7.0%). Estimates of the stroke rate at days 2, 7, 30, 90, and 365 were 1.5%, 2.1%, 2.8%, 3.7%, and 5.1%, respectively. These estimates were much lower than those compared with historical cohorts and were attributed to the widespread establishment of TIA clinics. Rothwell et al. (2007) reported that patients who had immediate access to a TIA clinic (EXPRESS) had a significantly reduced risk of recurrent stroke (2.1% vs.10.3%, p=0.0001), compared with an historical cohort who did not have immediate access to the same care. Patients with immediate access also received their prescriptions sooner (median of 1 vs. 20 days). Lavallée et al. (2007) reported the 90-day risk of stroke for all patients seen at their TIA-SOS clinic was lower than that predicted by their $ABCD^2$ score (1.24% vs. 5.96%).

Atrial fibrillation (AF) is a common arrhythmia, which is associated with an increased risk of ischemic stroke. Following minor stroke or TIA, detecting AF in patients with no previous history is important, particularly in those with a cryptogenic stroke or embolic stroke of unknown source. Once identified, AF can be effectively managed, typically with a switch from an antiplatelet to an anticoagulant. However, AF is under-diagnosed because it is frequently paroxysmal and asymptomatic, and patients do not routinely undergo prolonged screening. AF can be detected using a variety of methods including a12-lead electrocardiogram (ECG), Holter monitoring, event recorders and implantable devices. Low levels of monitoring were highlighted in a study authored by Edwards et al. (2016). The records of 17,398 consecutive patients presenting with first-ever stroke or TIA with motor or speech deficits, without a known history of AF in sinus rhythm, were reviewed and the utilization of ambulatory ECG monitoring within the first 90 days of the event was assessed. A total of 5,318 patients (30.6%) received at least 24-hour Holter monitoring within 30 days of the index event. The numbers associated with more prolonged Holter monitoring were lower; 2,253 patients (12.9%) and 25 patients (0.1%) underwent 48-hr and >60-hr monitoring, respectively within 90 days. Monitoring with event loop recording was conducted in 139 patients (0.8%) within 90 days. A meta-analysis conducted by Sposato et al. (2015) examined the use of outpatient cardiac monitoring following minor stroke or TIA in 4 distinct phases. The results from the studies that initiated investigations during the second ambulatory period (phase 4), using mobile cardiac outpatient telemetry (n=5), external loop recording (n=7) or implantable loop recording devices (n=7), reported an estimated 16.9% (95% CI 13.0% -21.2%) of patients were diagnosed with AF.

Prolonged ECG monitoring using wearable or insertable devices has been shown to be effective for improving the detection of paroxysmal AF (numbers needed to screen range from 8-14), with longer monitoring durations associated with an increased probability of AF detection. A systematic review and meta-analysis (Tsivgoulis et al. 2019) included the results from 2 RCTs (FIND-AF and Crystal AF and 2 observational studies). The outcomes of persons who received prolonged cardiac monitoring (PCM) using implantable cardiac monitoring or ambulatory ECG monitoring, were compared with patients who received conventional (non-PCM) cardiac monitoring. Among persons who received PCM, AF was detected more frequently (RR=2.46; 95% CI, 1.61–3.76), the risk of recurrent stroke and recurrent stroke or TIA during follow-up was significantly lower (RR=0.45; 95% CI, 0.21–0.97 and RR=0.49; 95% CI, 0.30–0.81, respectively) and anticoagulation therapy was initiated more frequently (RR=2.07; 95% CI, 1.36–3.17). In the FIND-AF trial, Wachter et al. (2016) recruited 398 patients, >60 years admitted with acute ischemic stroke, within 7 days of symptom onset, in sinus rhythm at admission and without a history of AF. Patients were randomized to receive prolonged Holter ECG monitoring for 10 days, starting in the first week post stroke, and repeated at 3 and 6 months or standard care (an average of 73 hours of inpatient telemetry plus an average of 24 hours of Holter monitoring). At both 6 and 12 months, detection of AF was significantly higher in the prolonged monitoring group (13.5% vs. 4.5% and 13.5% vs. 6.1%, respectively). The associated numbers needed to screen were 11 and 13. There were no significant differences between groups in stroke recurrence (2.5 vs. 4.5%, p=0.28) or death (3.0 vs. 4.5%, p=0.45). A UK trial (Higgins et al. 2013) that randomized 100 patients with no history of AF and in sinus rhythm, reported that a strategy of 7-day ECG monitoring in the acute phase post-stroke was superior to standard care for the detection of paroxysmal AF (18% vs. 2%; p<0.05). Significantly more patients that received additional monitoring were started on anticoagulants.

Among persons with nonacute stroke, Gladstone et al. (2014), found 30-day ambulatory cardiac event monitor to be superior to repeat 24-hour Holter monitoring in identifying AF in 572 patients aged 52 to 96 years without known AF, who had sustained a cryptogenic ischemic stroke or TIA within the

previous 6 months. Atrial fibrillation lasting ≥30 seconds was detected more frequently in persons using the cardiac event monitor (16.1% vs. 3.2%, absolute difference, 12.9%; 95% CI 8.0 to 17.6; p<0.001; number needed to screen= 8). The cardiac event monitor was also more likely to identify cases of AF lasting longer than ≥2.5 minutes (9.9% vs. 2.5%, absolute difference, 7.4%, 95% CI, 3.4 to 11.3; p<0.001). By 90 days, oral anticoagulant therapy had been prescribed for more patients in the intervention group (18.6% vs. 11.1%, p=0.01). Three-quarters of AF cases identified in the intervention group were detected within the first 2 weeks of monitoring.

The clinical and cost-effectiveness of prolonged ECG monitoring are likely greater for patients with estimated good life expectancy and quality of life, and for those with excessive atrial ectopy, enlarged or poorly contracting left atrium, or elevated natriuretic peptide levels. While prolonged post-stroke ECG monitoring improves AF detection, it should be noted that clinical trials have not been powered to determine the effect of prolonged ECG monitoring on the rate of recurrent stroke. Device-detected AF is often brief and subclinical and the minimum duration or burden of device-detected AF that warrants initiation of anticoagulant therapy remains uncertain; therefore, expert opinion varies widely.

It has been estimated that 5% of all people over the age of 65 years, in Canada, have evidence of vascular cognitive impairment (VCI). The reported prevalence tends to be higher in those individuals who have experienced a stroke, with up to 29% developing VCI over 5 years following stroke (Pendlebury et al. 2015). Therefore, patients should be screened at the time of presentation using validated instruments such as the Montreal Cognitive Assessment test (MoCA) or the Mini-Mental State Exam (MMSE).

Laboratory investigations and assessment of physiological variables as part of a patient's initial evaluation provides important information for patient management. A small case control study found that maintenance of normal physiological variables within the first three days of stroke has a beneficial effect on outcomes post stroke (Langhorne et al. 2000). Blood biomarkers have been shown to correlate with cerebral lesion size and stroke severity (Kisialiou et al. 2012). Ferrari et al. (2010) found that hypertension, diabetes, possible etiology, acute infection and cardiac abnormalities were all independent predictors of deterioration following TIA or minor stroke and recommended immediate diagnostic testing for their identification. Together, these findings suggest a complete evaluation of patients presenting with suspected stroke or TIA is beneficial for predicting risk of recurrent stroke and guiding patient management.
When in-hospital or in-clinic visits are not possible, some prevention interventions can be provided through virtual means, such as the telephone or computer-mediated communication. Virtual care interventions have been shown to effective for cardiovascular risk factor reduction. Monthly phone calls with a health advisor resulted in significantly lower systolic and diastolic blood pressures, and was also associated with significant improvements in diet, physical activity, drug adherence, and satisfaction with access to care, compared with usual care (Salisbury et al. 2016). Mobile health interventions were associated with a significantly reduced $HgbA1_C$ compared with the control condition and significantly increased odds of smoking cessation at 6 months (Liu et al. 2017). Digital health interventions including telemedicine, web-based strategies, email, mobile applications, text messaging, and monitoring sensors significantly reduced the risk of cardiovascular events (RR=0.61, 95% CI, 0.46–0.80, p<0.001) (Widmer et al. 2015).

Evidence Table and Reference List 1a: Triage and Initial Diagnostic Evaluation of Transient Ischemic Attack and Non-Disabling Stroke
Evidence Table and Reference List 1b: Virtual Care

TABLE 1A: Recommended Laboratory Investigations for Patients with Acute Stroke or Transient Ischemic Attack*

Note: This list presents the recommended initial laboratory tests for patients with stroke and transient ischemic attack. Patient presentation, clinical judgment, and local stroke protocols should be considered in selecting appropriate laboratory investigations and the timing of completion.

Recommended Laboratory Investigations for Patients with Stroke and Transient Ischemic Attack		
Complete Blood Count (CBC)	International Normalized Ratio (INR)	Partial Thromboplastin Time (PTT)
Electrolytes	Creatinine and glomerular filtration rate (eGFR)	Liver enzymes (e.g., AST, ALT)
Random Glucose or Hemoglobin A1C	Either a **fasting** plasma glucose, or 2-hour plasma glucose, or glycated hemoglobin (A1C), or 75 g oral glucose tolerance test	Lipid profile (Fasting optional and decision should be based on individual patient factors)

Additional Laboratory Investigations for Consideration in Specific Circumstances

Note: All patients are individuals, and some may require additional investigations to fully understand their clinical situation. The investigations noted below may not be indicated in many stroke patients and should be considered in selected stroke patients based on clinical presentation and medical history.

Optional Laboratory Investigations			
Calcium, Magnesium, Phosphate	If female less than 50 years of age, consider pregnancy test		Blood cultures if infection suspected (per individual institutional protocol)
ESR	CRP		Troponin, where indicated
Blood and/or urine drug screen		HIV, syphilis serology, where indicated	
Thrombophilia Screen – For consideration in selected patients *only if clinically indicated.* *Recommend consultation with a specialist in thrombosis to evaluate for hypercoagulable state*			
Anticardiolipin antibodies, Beta-2-glycoprotein	Lupus anticoagulant	Sickle cell screen	Serum homocysteine and vitamin B12
Venous Thrombosis Testing - **For consideration in selected patients *only if clinically indicated.*** *Recommend consultation with a specialist in thrombosis to evaluate for hypercoagulable state*			
Protein S	Protein C		Factor V Leiden
Prothrombin gene mutation		Antithrombin III	
Special considerations especially in young adults and children with stroke in absence of identified etiology *(Note there is not a strong evidence base for these investigations, and they should be considered only in selected stroke patients based on clinical presentation and medical history.)* ***Consultation with a hematologist or neurologist is recommended.***			
Consider LP for CSF analysis (cell count and differential, protein, glucose, bacterial and viral studies; possibly cytology/flow cytometry if CNS lymphoma is a consideration)		Brain biopsy (if vasculitis of the central nervous system or angiocentric lymphoma is a consideration)	
Catheter cerebral angiography		Further genetic tests – CADASIL, Fabry's, MELAS	

2. Lifestyle Behaviours and Risk Factor Management

Note: These recommendations are applicable to stroke of ischemic, hemorrhagic and transient ischemic attack in origin unless otherwise stated.

Section 2 Recommendations 2020

2.1 Risk Factor Assessment:

i. Persons at risk of stroke and patients who have had a stroke or transient ischemic attack 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 transient ischemic attack 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 behaviours and choices where required [Evidence Level B].

2.2 Healthy Balanced Diet

i. Counsel and educate individuals with transient ischemic attack 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]. *Refer to Canada's Food Guide for additional information.*

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

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 fibre 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]. *Refer to Section 2.3 for details*.

Section 2.2 Clinical Consideration

i. 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 transient ischemic attack 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]. *Refer to the Hypertension Canada 2020 Guidelines on Health Behaviour Management for additional information.*

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 behaviour to adapt appropriately. (https://www.canada.ca/en/health-canada/services/food-nutrition/healthy-eating/sodium.html)

2.4 Physical Activity

Refer to CSBPR Rehabilitation and Recovery Module 2020 Section 6 and the AEROBICS 2020 Update for additional information

i. Counsel and educate individuals with transient ischemic attack or stroke to reduce sedentary behaviors and sedentary time, and to work towards 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 transient ischemic attack or stroke to participate in aerobic exercise 4 to 7 days per week, to accumulate at least 150 minutes per week in episodes of 10 minutes 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 transient ischemic attack 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

i. Aerobic exercise intensity should be individualized. Factors to consider include functional limitation, co-existing medical problems such as cardiac disease, need for an exercise stress test with electrocardiogram, and planned exercise intensity (i.e., light, moderate, or vigorous).

ii. Screening and supervision of adults with comorbid disease such as cardiac disease which places them at higher risk of medical complications should be considered.

iii. 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 transient ischemic attack or stroke to achieve and maintain a waist circumference of <88 centimeters for women and <102 centimeters for men*, or a body mass index (BMI) of 18.5 to 24.9 kg/m^2 [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 transient ischemic attack 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 behavioural interventions [Evidence Level B].

Section 2.5 Clinical Consideration

i. When discussing weight, consider completion of a comprehensive history that explores root causes of weight gain and avoids stigma and judgment. *Refer to 2020 Canadian Obesity Network guidelines for additional information.*

2.6 Alcohol Consumption

i. Counsel and educate individuals with transient ischemic attack 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 transient ischemic attack 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.

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

i. 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. *Refer to 2020 Canada's Lower-Risk Cannabis Use Guidelines (hyperlink) (Fischer et al 2017; DOI: 10.2105/AJPH.2017.303818.)*

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 behavioural 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 where it is not covered under a provincial drug formulary [Evidence Level C]. *Refer to Appendix Three: Pharmacotherapy in Smoking Cessation Treatment.*

   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]. *Refer to Implementation Resources below for the Ottawa Model as an example of protocol tool.*

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]. *Refer to Implementation Resources below for Motivational interviewing tools.*

Section 2.8 Clinical Considerations

Use of E-Cigarettes

i. While some individuals may find vape products helpful in smoking cessation, the evidence base around their population-based effectiveness is not clear.

ii. 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. (ref: Hajek P, Phillips-Waller A, Przulj D, et al. *N Engl J Med*. 2019

iii. Emerging evidence indicates an association between vaping and elevated blood pressure; the strength of the association is not clear at this time.

iv. 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".

v. 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.

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]. *Refer to CSBPR Secondary Prevention of Stroke during Pregnancy recommendations for additional information.*

ii. Contraception should be addressed based upon the patients' fertility and pregnancy plans as well as the stroke mechanism and type [Evidence Level C]. *Refer to CSBPR Secondary Prevention of Stroke during Pregnancy recommendations for additional information.*

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 transient ischemic attack or ischemic stroke [Evidence Level B]. Management alternatives should be considered in these patients [Evidence Level C]. *Refer to Society of Obstetrics and Gynecology of Canada*

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]. (ref: ACOG 2019; McClester 2013)

vii. **Hypertensive Disorders of Pregnancy**: Discussion on the use and dose of 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].

Refer to Hypertension Canada 2020 recommendations Section 3 for additional information on hypertension in pregnancy. Refer to Society of Obstetricians and Gynecologists current guidelines of Obstetricians and Gynecologists current guidelines.

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].

2.12 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].

Rationale

A healthy lifestyle reduces the risk of an initial stroke and the risk of a subsequent stroke for patients with a prior stroke. Hypertension is the single most important modifiable risk factor for stroke. Current research reports estimate that reducing sodium in foods would abolish high blood pressure for almost one in three Canadians. Most of the sodium Canadians consume (77%) comes from processed foods sold in grocery stores and food service outlets. Only about 11% is added during preparation or at the table, with the remainder occurring naturally in foods. Available evidence suggests that lowering sodium consumption to adequate intake levels could reduce the incidence of stroke and heart disease by as much as 30 percent and has a significant impact on lowering blood pressure. Data from Global Burden of Disease Study (Feigin et al. 2016) estimated that in Canada, 12.6% of the stroke burden was attributed to diets high in sodium.

The evidence for the benefits of exercise in reducing the risk of stroke and other vascular diseases has increased considerably in the past several years. The 2020 Canadian 24-hour Movement Guidelines for Adults implement a balanced approach to including exercise, sleep and reduced sedentary behaviours as part of their new recommendations, as these have all been associated with improved mortality and morbidity in adults (Ross et al, 2020).

There is a growing concern for obesity in the Canadian population, especially in younger adults and this must be addressed with all patients with stroke or at risk. Data from Global Burden of Disease Study (Feigin et al. 2016) reported that in Canada 28.4% of the stroke burden was attributed to a high BMI. Obesity may be result of an obesogenic food environment which includes frequent high exposure to high fat, sugars, calories, etc. Saturated fat increases LDL-cholesterol levels in the blood. High LDL-cholesterol is a risk factor for heart disease and stroke. Replacing saturated fats with mono- and poly-unsaturated fats decreases LDL-cholesterol. It is estimated that Canadians consume approximately 10% of their total calorie intake from saturated fats. Highly processed foods are a major source of saturated fat in the Canadian diet. These highly processed foods are also high in calories, sodium, and free sugars, and can be high in other types of unhealthy fats like trans fatty acids (trans fats). Canadian estimates have been reported for burden attributed to several stroke risk factors, including for tobacco use (13% of stroke burden), alcohol use (7.7%), low physical activity (10.9%), low fruit intake (20.4%), low vegetables intake (19.5%).

The Quality of Stroke Care in Canada stroke audit report found that among all Canadians who experienced a stroke in 2008-09, 41% were current smokers, and more prominent in younger adult stroke patients (less than 49 years old). The InterStroke study reported that current smokers had increased risk of stroke, with the impact greater on ischemic stroke compared to hemorrhagic stroke, and this risk increased with the number of cigarettes smoked per day. Also, the significant impact of smoking on stroke was second only to hypertension. The 2019 Canadian Community Health Survey has reported that approximately 14.8% of people in Canada (age 12+) are current smokers, and a large proportion has been shown to be willing to make a quit attempt. Health care providers have an important role to play in assisting individuals to quit smoking. Moreover, even brief interventions by providers are known to be effective in increasing the likelihood of a quit attempt by a person who smokes. Clinical practice guidelines are known to be an important and effective provider tool to close

the gap between recommended care and actual care provided. Smoking cessation has been found to reverse/reduce stroke risk as duration of being smoke-free increased.

Female patients who have had a stroke are at additional risk for recurrent stroke if they continue to smoke and are taking oral contraception or estrogen-based hormone replacement therapy. Research has also demonstrated an increased risk of thrombosis with estrogen-based hormone therapy (both oral contraceptives and hormone-replacement therapy).

People with stroke, their family members and caregivers expressed the need to have risk factor management information early on after the stroke occurs. Many of these individuals have expressed concerns that they did not receive this information until significant time had passed or had not received this information at all. This issue highlights a potential disconnect between people with stroke and their health care team after transition to living in the community, and potential disconnect between their primary healthcare provider and the other health professionals involved in their care, such as the stroke expert and rehabilitation team members.

People with stroke have also voiced the difficulty in managing and tracking lifestyle behaviour changes and knowing what targets are appropriate for them. Education on how to manage these risk factors is essential along with easy-to-use tools to support their efforts. People with stroke also emphasized the need to individualize the interventions to be able to successfully work on these risk factors. Some people with stroke have difficulty with physical exercise due to other conditions and needed their exercise routine individualized to meet their unique needs. Feedback from people with stroke also included the need for individualization of strategies that incorporate other health issues that may be experiencing, as multimorbidity is becoming increasingly common among people with stroke (Heart & Stroke Disconnected Report, 2019).

System Implications

1. Health promotion efforts that contribute to the prevention of stroke in all communities (integrated with existing chronic disease prevention initiatives) must be established.
2. Coordinated and comprehensive stroke prevention should be offered by primary care providers, and a mechanism in place to ensure that stroke risk is addressed during encounters with healthcare professionals throughout the continuum of care.
3. Improved communication and transition planning between all stages and settings of care and ensuring that primary care team members are fully informed on the goals of care, prevention therapies initiated by the healthcare providers during first assessments (e.g., in the emergency department), follow-up appointments for further investigations and longterm management.
4. Public and population health focus on cerebrovascular health for paediatric cases focus on risk reduction through diet, - including limited saturated fat, sodium and sugar intake, - physical activity, non-smoking, avoidance of drugs that increase stroke risk.
5. Regional, national, and international efforts to reduce sodium intake by working with governments and changing the food supply in both the food retail and restaurant sector are required.
6. Increase public awareness and knowledge about the risks of sodium through targeted and population-based campaigns. School programs which teach food literacy including cooking from scratch using whole, minimally processed foods. Promote mandatory front of package nutrition labelling to help increase public awareness, knowledge, improve decision making and encourage product reformulation.
7. Local, regional, and federal food strategies which improve access to and affordability of whole unprocessed foods in all communities.
8. Access to risk factor management programs (such as hypertension and smoking cessation programs) in all communities, primary healthcare settings and workplaces.

9. Improved best practice cessation support through pharmacotherapy, nicotine replacement therapy and behavior counselling. Access to these types of interventions can be facilitated through a universal pharmacare program.
10. Government action at all levels of government to reduce tobacco use. Consider WHO MPOWER tobacco control strategy as a framework. (https://www.who.int/tobacco/mpower/en) which emphasizes in the guiding principles that smokers should be granted access to smoking cessation support without financial burdens.
11. Coordinated efforts among stakeholders such as the Heart and Stroke Foundation, public health agencies, ministries of health and care providers across the continuum to produce patient, family and caregiver education materials with consistent information and messages on risk factor management.
12. Coordinated processes for ensuring access to and awareness of educational materials, programs, activities and other media related to risk factor management by healthcare professionals, patients and caregivers, including promotion of educational material and effective dissemination mechanisms.
13. Improved access to pharmaceuticals and behavior counselling for smoking cessation through private and public drug coverage plans.
14. Government action at all levels of government to reduce tobacco use.
15. Government regulation of e-cigarettes, including flavours restrictions and nicotine limits, taxation, raising the legal of purchase to 21 years, prohibiting the use of e-cigarettes in workplaces and public places where smoking is banned by law and e-cigarette sales in locations where tobacco sales are banned.
16. Access to culturally and ethnically appropriate educational resources in multiple languages as well as special resources for patients with aphasia.
17. Increased infrastructure investments in communities that facilitate physical activity. This should include recreational infrastructure (such as recreation centres, arenas) and active transportation infrastructure (e.g., sidewalks, bike paths).
18. Access to healthy living programs, educational materials and healthcare professionals for persons living in rural and remote locations, including innovative use of technology and virtual healthcare.
19. Increased measures to reduce air pollution.
20. Integration of air pollution considerations into disease management approaches, for example through the use of air quality indices.
21. Access to education and efforts to raise awareness on the cardiovascular benefits of clean air.
22. If the community doesn't have regular access to rehabilitation services (such as physiotherapy), could there be encouragement to connect to another facility that provide the service. What level of supervision is available – communities may have other options.

Performance Measures

1. Proportion of patients with major risk factors for stroke, including hypertension, obesity, hyperlipidemia, diabetes, atrial fibrillation, smoking, and physical inactivity. (KQI)
2. Annual occurrence rates for stroke in each province and territory by stroke type (KQI).
3. Proportion of acute stroke and transient ischemic attack patients who are discharged alive from an emergency department or an inpatient stay and then readmitted to hospital for any cause within 7 days of index acute stroke discharge. (KQI)

4. Stroke mortality rates across provinces and territories, including in-hospital or 30-day rate and one-year rate (KQI).
5. Percentage of the population who can identify the major risk factors for stroke, including hypertension, sodium intake, diet, weight, exercise, smoking and alcohol intake.
6. The annual readmission rate for a recurrent stroke or transient ischemic attack event in patients with previous stroke or transient ischemic attack.
7. Proportion of patients with documented smoking status recorded on patient record.
8. Proportion of patients with stroke and transient ischemic attack with a history of tobacco smoking who are given smoking cessation advice and counselling during acute hospital stay, inpatient and outpatient rehabilitation, and during secondary prevention visits.
9. Proportion of stroke and transient ischemic attack patients who participate in a smoking cessation program who are smoke-free at 6 months, one year and two years.

Measurement notes

1. For performance measures 1, 2 and 3: self-reported data can be extracted from provincial and national health surveys. These data should be standardized to the most current national census data for age and sex.
2. Performance measures 4: administrative data are available at the local, provincial and national levels.
3. Mortality rates should be risk adjusted for age, sex, stroke severity and comorbidities.

Implementation Resources and Knowledge Transfer Tools

Health Care Provider Information

- Heart & Stroke: FAST Signs of Stroke: https://www.heartandstroke.ca/stroke/signs-of-stroke/fast-signs-of-stroke-are-there-other-signs
- CSPBR: Secondary Prevention of Stroke During Pregnancy: https://www.strokebestpractices.ca/recommendations/prevention-of-recurrent-stroke-in-pregnancy
- CSBPR: Secondary Prevention of Stroke: Appendix Three: Pharmacotherapy for Smoking Cessation
- CSBPR Virtual Healthcare Toolkit https://www.heartandstroke.ca/-/media/1-stroke-best-practices/csbpr7-virtualcaretools-13may2020
- Heart & Stroke: Post-Stroke Checklist: https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/002-17_csbp_post_stroke_checklist_85x11_en_v1
- CSBPR Virtual Healthcare Toolkit https://www.heartandstroke.ca/-/media/1-stroke-best-practices/csbpr7-virtualcaretools-13may2020
- Heart & Stroke: Sugar position statement: https://www.heartandstroke.ca/-/media/pdf-files/canada/2017-position-statements/sugar-ps-eng
- Heart & Stroke: Smoking and tobacco: https://www.heartandstroke.ca/heart-disease/risk-and-prevention/lifestyle-risk-factors/smoking-and-tobacco
- Hypertension Canada Guidelines: https://guidelines.hypertension.ca/chep-resources/

- Government of Canada: Canada's Food Guide: https://food-guide.canada.ca/en/
  - Resources: https://food-guide.canada.ca/en/healthy-eating-resources/
- Government of Canada: Recommended intake for sodium table: https://www.canada.ca/en/health-canada/services/food-nutrition/healthy-eating/sodium.html#a2
- CSEP: Canadian Physical Activity Guidelines for Adults 18-64 years old https://csepguidelines.ca/adults-18-64/
- CSEP: Canadian Physical Activity Guidelines for Older Adults 65 years and older https://csepguidelines.ca/adults-65/
- Obesity Canada: Canadian Adult Obesity Clinical Practice Guidelines: https://obesitycanada.ca/guidelines/chapters/
- Canadian Best Practice Recommendations for Stroke Care Smoking Cessation Pharmacology Summary Table: Appendix 3
- University of Ottawa Heart Institute: Ottawa Model for Smoking Cessation
  - https://ottawamodel.ottawaheart.ca/about-omsc
  - E-learning, workshops and other resources: https://ottawamodel.ottawaheart.ca/education
- CADTH Smoking Cessation Pharmacology https://www.cadth.ca/pharmacologic-based-strategies-smoking-cessation-clinical-and-cost-effectiveness-analyses
- CAMH Nicotine Dependence Clinic: https://www.camh.ca/en/your-care/programs-and-services/nicotine-dependence-clinic https://www.nicotinedependenceclinic.com/en/teach/practitioner-resources/teach-tool4
- RNAO: Integrating Tobacco Interventions into Daily Practice https://rnao.ca/bpg/guidelines/integrating-tobacco-interventions-daily-practice
- The Society of Obstetricians and Gynecologists of Canada: https://sogc.org/en/guidelines-and-jogc/Guidelines/en/content/guidelines-jogc/guidelines-and-jogc-new.aspx?hkey=2b49bce7-cc2d-494d-9f5d-a6e0bbfff9c5
- Government of Canada: Canada's lower-risk cannabis use guidelines: https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/resources/lower-risk-cannabis-use-guidelines.html
- Canada's Low-Risk Alcohol Drinking Guidelines: https://www.ccsa.ca/canadas-low-risk-alcohol-drinking-guidelines-brochure
- Government of Canada – Sleep Apnea: https://www.canada.ca/en/public-health/services/chronic-diseases/sleep-apnea.html
- Depression, Obstructive Sleep Apnea and Cognitive Impairment – DOC Screening Tool http://www.docscreen.ca/about.html

Patient Information

- Heart & Stroke: FAST Signs of Stroke: https://www.heartandstroke.ca/stroke/signs-of-stroke/fast-signs-of-stroke-are-there-other-signs
- Heart & Stroke: Are you at risk for heart disease or stroke?: https://www.heartandstroke.ca/-/media/pdf-files/canada/health-information-catalogue/en-are-you-at-risk
- Heart & Stroke: Post-Stroke Checklist:

https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/002-17_csbp_post_stroke_checklist_85x11_en_v1

- Heart & Stroke: Your Stroke Journey: https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/en-your-stroke-journey-v21
- Heart & Stroke: Taking charge of your stroke recovery: 2020 Virtual healthcare checklist infographic: https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/csbp-infographic-virtual-healthcare-checklist
- Heart & Stroke: Working with your doctor: www.heartandstroke.ca/heart-disease/recovery-and-support/working-with-your-doctor
- Heart & Stroke: Risk and prevention https://www.heartandstroke.ca/stroke/risk-and-prevention
- Heart & Stroke: Healthy Weight: https://www.heartandstroke.ca/healthy-living/healthy-weight?_ga=2.235559361.1157019632.1611585537-2092542146.1608572095
- Heart & Stroke: How to take a proper waist measurement: https://www.heartandstroke.ca/healthy-living/healthy-weight/healthy-weight-and-waist
- Heart & Stroke: Smoking and tobacco information: https://www.heartandstroke.ca/heart-disease/risk-and-prevention/lifestyle-risk-factors/smoking-and-tobacco
- Heart & Stroke: Healthy Living Information https://www.heartandstroke.ca/healthy-living
- Heart & Stroke Resource on specific diets (DASH, vegetarian, Mediterranean, MIND): https://www.heartandstroke.ca/healthy-living/healthy-eating/specific-diets
- Heart & Stroke Resource on DASH diet:

  https://www.heartandstroke.ca/healthy-living/healthy-eating/dash-diet
- Heart & Stroke: Online and Peer Support https://www.heartandstroke.ca/heart-disease/recovery-and-support/the-power-of-community
- Government of Canada: Canada's Food Guide Health Eating Resources https://food-guide.canada.ca/en/healthy-eating-resources/
- Mayo Clinic - Mediterranean diet http://www.mayoclinic.com/health/mediterranean-diet/CL00011
- Tobacco Quit Line: 1-866-366-3667
- Break it off: http://breakitoff.ca/
- Smokers Helpline online program: http://www.smokershelpline.ca/
- Health Canada: Quit Smoking: https://www.canada.ca/en/health-canada/services/smoking-tobacco/quit-smoking.html
- Quit Now: https://www.quitnow.ca/
- Lung Association: https://www.lung.ca/lung-health/smoking-and-tobacco
- Canada's Low-Risk Alcohol Drinking Guidelines: https://www.ccsa.ca/canadas-low-risk-alcohol-drinking-guidelines-brochure

Summary of the Evidence 2020

Lifestyle and Risk Factor Management

Diet

Adherence to several dietary eating patterns has been examined in the context of stroke risk. Among them, the Dietary Approaches to Stop Hypertension (DASH) and the Mediterranean Diet are two of the most recognized. Feng et al. (2018) included the results of 12 prospective cohort studies including 548,632 participants. During follow-up, which ranged from 5.7 to 24 years, higher adherence to the DASH diet significantly reduced the risk of stroke (RR=0.88, 95% CI 0.83-0.93). Each 4-point increment in DASH score conferred a risk reduction of 4% (RR= 0.96, 95% CI 0.94–0.97) in total stroke events. Larsson et al. (2016) also reported that high adherence to a modified DASH diet was associated with a reduced risk of ischemic stroke, particularly among women. The study included a population-based sample of almost 75,000 individuals without history of stroke, heart disease or cancer, who were followed for an average of 11.9 years.

A systematic review & meta-analysis conducted by Psaltopoulou et al. (2013), including the results of 11 studies, concluded that high adherence to a Mediterranean diet was associated with reduced risk of total stroke and ischemic stroke (total stroke: RR=0.71, 95% CI 0.57-0.89; ischemic stroke: RR=0.52, 95% CI 0.28-0.96). One of the key components of the Mediterranean diet is olive oil, which has been shown to decrease the risk of cardiovascular diseases. The Prevención con Dieta Mediterránea Trial (PREDIMED) evaluated the benefits of 2 types of Mediterranean diet, increased consumption of extra-virgin olive oil or mixed nuts, as compared to a control group in which participants were advised to follow a low-fat diet (Estruch et al. 2013). After a median follow-up of 4.8 years, the two Mediterranean diets were associated with 30% reductions in the primary outcome, a composite of myocardial infarction, stroke, or death from cardiovascular causes. Most of this protective effect was driven by a reduction in stroke events. The results of the PREDIMED study were included in a systematic review (Martınez-Gonzalez et al. 2014) specifically examining the protective effect of olive oil. For each 25 g/day increase in olive oil consumption there was a significant reduction in the risk of stroke (RR=0.76, 95% CI 0.67-0.86, p<0.001).

Sodium

It is well documented that a consistently high dietary sodium intake is associated with elevated blood pressure, while modest decreases may lower blood pressure and reduce stroke risk. Mozaffarian et al. (2014) used various data sources and national-level surveys to estimate that, in 2010, 99% of all adults in the world exceeded the WHO recommendations of 2.0 g/day. Worldwide, the mean global level of sodium intake was 3.95 g/day. An estimated 1.65 million deaths were attributed to sodium intake above the recommended level, of which 685K (42%) were caused by stroke. In one of the PURE publications, Mente et al. (2018) estimated that for each 1-gram increase in estimated sodium intake, systolic BP increased by 2·86 mm Hg (95% CI 2·12–3·60, p<0·0001). Feigin et al. (2016) estimated that 22.6% of the global stroke burden was attributed to diets high in sodium (12.6% in Canada). In a Cochrane review, He et al. (2013) examined 34 RCTs (n=3,230) comparing the effect of moderately restricted sodium intake (2.3-7.0 g/day or 40-120 mmol/day urinary sodium excretion) for a minimum of 4 weeks with usual intake over the same duration. The mean difference in sodium intake between groups was 1,955 mg per day, which was associated with a significant decrease in SBP (-4.18 mm Hg, 95% CI -5.18 to -3.18; p<0.001) and DBP (-2.06 mm Hg, 95% CI -2.67 to -1.45; p<0.001). Results were similar in a subgroup analysis of 22 trials that included 990 patients with hypertension. Reduced intake was associated with a significant reduction in both SBP (-5.39 mm Hg, 95% CI -4.15 to -6.62; p<0.001) and DBP (-2.82 mm Hg, 95% CI -2.11 to -3.54; p<0.001).

Physical Activity

Physical activity (PA) is an important modifiable lifestyle factor that can play a protective role in both primary and secondary prevention of stroke. Using data from 188 countries, obtained from the Global Burden of Disease Study, Feigin et al. (2016) reported that 7.7% of the global stroke burden was attributed to low physical activity. In Canada, the estimate was 10.9%. The results from several large cohort studies provide some estimates of the magnitude of the protective effect of physical activity. In one of the PURE publications, Lear et al. (2017) included 130,843 participants without pre-existing cardiovascular disease, aged 35-70 years (mean age 50.2 years). After an average of 6.9 years of follow-up, the risk of all-cause mortality and major cardiovascular disease was reduced significantly among persons who engaged in high levels of moderately intense physical activity (>750 minutes/week) and moderate amounts (150-750 minutes /week) compared with those who engaged in low levels of physical activity (<150 minutes/week). In phase 1 of the INTERSTROKE case-control study, O'Donnell et al. (2010) reported that regular physical activity was associated with a reduced risk of total and ischemic stroke (total stroke: OR=0.69, 99% CI 0.53-0.90, ischemic stroke: OR=0.68, 99% CI 0.51-0.91). In phase 2 of the INTERSTROKE study (O'Donnell et al. 2016), the pattern of results was similar.

Weight

There is an increased risk of stroke associated with being overweight or obese. Feigin et al. (2016) reported that 23.5% of the global stroke burden was attributed to high BMI (>23.0), while in Canada the estimate was 28.4%. Twig et al. (2016) included 2.3 million adolescents who were followed over time to examine the association between BMI and cardiovascular death. During 42,297,007 person-years of follow-up, there were 32,127 deaths, including 528 from stroke. Compared with the reference category (BMI percentile 5^{th}-24^{th}), the risk of death from stroke was significantly increased in the 3 highest BMI categories, in which the median BMI (men and women combined) were 24.4, 26.6 and 31.0, respectively (75^{th}-85^{th}: HR=1.42, 85^{th}-94^{th}: HR=1.81, ≥95^{th}: HR=2.64). Saito et al. (2011) compared stroke risk in 32,847 men and 38,875 Japanese women, aged 45–74 years with no history of cardiovascular disease, who were of normal weight (BMI 23.0-24.9 kg/m^2) with persons who had high BMIs (27.0 to 29.9 and ≥ 30.0). The risk of stroke significantly increased with increasing BMI (HR= 1.09 and 1.25 for men, and HR=1.29 and 2.16 for women, respectively, relative to healthy weight). In women, a weight increases of greater than 10% over the previous five years was also associated with increased stroke risk. In phases 1 and 2 of the INTERSTROKE case-control study, O'Donnell et al. (2010, 2016) reported that increasing waist-to-hip ratio was associated with increased risk of total stroke, ischemic stroke and hemorrhagic stroke.

Alcohol Consumption

Evidence from several studies suggest that light to moderate alcohol consumption may reduce the risk of stroke, while excessive consumption may increase risk. In the China Kadoorie Biobank Prospective study (Millwood et al. 2019) included 512,715 adults from 10 areas in China, aged 35-74 years, without known major disabilities, to examine the effect of alcohol consumption on cardiovascular disease risk. Among men, 33% reported drinking alcohol in most weeks, mainly as spirits. Using conventional epidemiological analysis, the risk of stroke was U-shaped, whereby the relative risk of total stroke was 1.23 (95% CI 1.19, 1.27) for non-drinkers, compared with 1.00 (95% CI 0.98-1.03) for occasional drinkers. Among current drinkers, the risks of ischemic stroke, ICH and total stroke were all significantly increased (when intake exceeded 100 g per week). Per each 280 g per week increase in alcohol intake, the risks of ischemic stroke ICH and total stroke were all significantly increased (RR= 1·28, 95% CI 1·19–1·38; HR= 1·59, 95% CI 1·37–1·85 and RR= 1·35, 95% CI 1·27–1·44, respectively). In

contrast, there was no U-shaped pattern using genotype-predicted mean alcohol intake, whereby the risk of ischemic stroke, ICH and total stroke increased across the whole range of mean alcohol intakes (RR= 1·27, 95% CI 1·13–1·43, RR= 1·58, 95% CI 1·36–1·84 and RR= 1·38, 95% CI 1·26–1·51, respectively). In women, the risks of ischemic stroke, ICH, total stroke, acute myocardial infarction (MI) and coronary heart disease (CHD) were not increased with alcohol consumption in either the conventional analysis, nor genetic analysis, although only 2% of women reported drinking alcohol most weeks. Zheng et al. (2015) pooled the results from 23 cohort studies and found that, compared with the lowest or no alcohol groups, the risk of stroke was not significantly increased in men or women as alcohol consumption increased; rather, the risk of ischemic stroke was lower in men who were light drinkers and for women who were light or moderate consumers. In contrast, using the results from 26 studies, O'Donnell et al. (2010) reported that moderate alcohol consumption (1-30 drinks/month) was associated with reduced risk of ischemic stroke (OR=0.79, 95% CI 0.63-1.00), but with an increased risk of hemorrhagic stroke (OR=1.52, 95% CI 1.07-2.16) compared with never/former drinkers. Binge drinking, or >30 drinks/month, was associated with an increased risk of ischemic and hemorrhagic stroke compared with never/former drinkers. In phase 2 of INTERSTROKE (O'Donnell et al. 2016) low or moderate ETOH intake was associated with significantly higher odds of total and hemorrhagic stroke compared with former/never drinkers, with no risk in the increase of ischemic stroke.

Recreational Drug Use

The most commonly used illicit drugs associated with increased stroke risk are cocaine, amphetamines, Ecstasy, heroin/opiates, phencyclidine (PCP), lysergic acid diethylamide (LSD), and cannabis/marijuana. These drugs may increase the risk for stroke through a variety of mechanisms, including hypertensive surges, vasospasm, enhanced platelet aggregation, vasculitis, accelerated atherosclerosis and cardioembolism. Using data from 3,307,310 young adults 18-49 years, who were hospitalized between 2007 and 2014 in the USA, and who were current or previous cannabis users, Desai et al. (2019) reported the odds of any stroke and ischemic stroke were increased significantly among cannabis users compared with non-users (adj OR= 1.16, 95% CI 1.14–1.19, p<0.001 and adj OR= 1.41, 95% CI 1.31–1.51, p<0.001), among 34,857 (1.1%) hospitalizations that were stroke related. In contrast to these findings, Luis et al. (2020) reported that recent marijuana use was not an independent predictor of acute ischemic stroke.

Cheng et al. (2016) examined whether recent cocaine use increased the risk of stroke. Cocaine use within 24 hours of the reference date was associated with a significantly increased risk of ischemic stroke (OR=6.4, 95% CI 2.2-18.6, p<0.001), as was frequent use (≥1/week; OR=2.6, 95% CI 1.6-4.3, p<0.001). An increased risk of stroke associated with cocaine use was also reported by Westover et al. (2007) in a cohort of patients recently discharged from hospital. Previous cocaine use was associated with an increase in the risk of both hemorrhagic and ischemic stroke (OR=2.33, 95% CI 1.74-3.11and OR=2.03, 95% CI 1.48-2.79, respectively). In the same study, amphetamine use was also associated with an increase in the risk of hemorrhagic stroke (OR=4.95, 95% CI 3.24-7.55) and an increased risk of hemorrhagic stroke resulting in death (OR=2.63, 95% CI 1.07-6.50).

Smoking

Smoking is a major risk factor for cardiovascular disease, including stroke and heart attacks. Smokers are significantly more likely to have a stroke compared with non-smokers. It has been estimated that globally, 20.7% of the stroke burden is attributable to tobacco use (Feigin et al. 2016). A systematic review & meta-analysis (Peters et al. 2013) reported sex-specific risks of current smokers vs. non-smokers including the results from 81 prospective cohort studies, which represented 3,980,359 persons. The prevalence of current smoking ranged from 8% to 59% in men and from 1% to 51% in women. Most studies reported higher smoking rates among men. Over the duration of follow up, which

ranged from 6-40 years, there were 42,401 strokes. The risk of stroke was higher in current smokers compared with non-smokers in both women: (RR=1.83, 95% CI 1.58-2.12) and men (RR=1.67, 95% CI 1.49-1.88). The risk of stroke was also higher in former smokers compared with never smokers (women: RR=1.17, 95% CI 1.12-1.22; men: RR=1.08, 95% CI 1.03-1.13). The risk of hemorrhagic, but not ischemic stroke, was significantly increased in women who smoked compared with men who smoked (RR=1.17, 95% CI 1.02-1.34, p=0.02). In phase I of the INTERSTROKE study (O'Donnell et al. 2010), there was an increased risk of all stroke (OR=2.09, 99% CI 1.75-2.51), ischemic stroke (OR=2.32, 99% CI 1.91-2.81) and hemorrhagic stroke (OR=1.45, 99% CI 1.07-1.96) associated with current smoking. In phase 2 of the study (O'Donnell et al. 2016), which included a larger sample size (26,919), the risk of ischemic stroke was higher among current smokers compared with the risk of hemorrhagic stroke (OR=1.93, 99% CI 1.69-2.21 vs. OR=1.14, 99% CI 0.95-1.36). The risk of both stroke types increased with the number of cigarettes smoked daily.

Both pharmacological agents and behavioural intervention strategies have proved effective as smoking cessation interventions. A Cochrane review (Hartmann-Boyce et al. 2018) included the results of 136 RCTs (n=64,640) of current smokers who were people motivated to quit. Trials compared nicotine replacement therapy (NRT) including chewing gum (n=56), transdermal patches (n=51), nasal (n=4) or oral spray (n=5), inhalators and tablets or lozenges (n=8), and combinations of NRTs to placebo or no treatment. Overall, the use of all forms of NRT was associated with a significantly increased likelihood of successful smoking cessation (RR=1.55, 95% CI 1.49 to 1.61), with little effect of type of NRT, while intensive behavioural support was not found to be essential for NRT to be effective. Another Cochrane review (Stead et al. 2015) examined the use of behavioral therapy support as an adjunct to pharmacotherapy and reported that more intensive behavioural support was associated with a better chance of long-term abstinence from smoking when combined with pharmacotherapy, as compared to pharmacotherapy combined with less intensive behavioural support (RR= 1.17, 95% CI 1.11 to 1.24). An earlier Cochrane review of reviews examined the effectiveness of pharmacological treatments to promote smoking cessation in adults included the results of 12 Cochrane reviews, aggregating the results from 267 RCTs, 101,804 participants (Cahill et al. 2013). Treatments evaluated included nicotine replacement products, such as gums, transdermal patches, nasal sprays or inhalers, the non-tricyclic antidepressant, bupropion and varenicline, a nicotinic receptor partial agonist. Compared with placebo, all forms of therapies significantly increased the odds of sustained smoking cessation (odds ratios ranged from 1.82-2.88). Varenicline was superior to single forms of nicotine replacement therapy (OR= 1.57, 95% Credible interval [Cred I] 1.29 to 1.91) and was also superior to bupropion (OR= 1.59, 95% CredI 1.29 to 1.96). The odds of serious adverse events (chest pains and heart palpitations) associated with nicotine replacement therapy were significantly increased (OR= 1.88, 95% CI 1.37-2.57). The most common side effects associated with bupropion were insomnia, occurring in 30% to 40% of patients, dry mouth (10%) and nausea. The main serious adverse event was seizures. The main adverse event for varenicline was mild-moderate nausea, which subsided over time and was rarely reported. Typical drop-out rates due to adverse events ranged from 7% to 12%.
Mullen et al. (2016) examined the use of the Ottawa Model' for Smoking Cessation (OMSC), a systematic approach to tobacco dependence treatment delivered within healthcare settings, which included in-hospital counselling, and pharmacotherapy follow-up support post hospitalization. At one and two years, the cumulative incidences of death and all-cause re-hospitalizations, and smoking-related readmissions were significantly lower in the OMSC group. All-cause emergency department visits were also significantly reduced in the intervention group. In this trial patients in the control group were randomized to usual care, which generally consisted of a self-help pamphlet.

The use of electronic cigarettes (e-cigarettes) has increased in recent years. They may be used as an

alternative to conventional cigarettes or as an aid in smoking cessation programs. The use of e-cigarettes has been shown to significantly reduce the use of conventional cigarettes, compared with nicotine-replacement products (Hajek et al. 2019). In this RCT that randomized 886 adult smokers to receive nicotine patches or e-cigarettes, provided for up to three months, the one-year abstinence rate was significantly higher in the e-cigarette group (18.0% vs. 9.9%; RR=1.83; 95% CI, 1.30 to 2.58; p<0.001). A Cochrane review (Hartmann-Boyce et al. 2016) included the results of two RCTs and 11 cohort studies including participants who were current smokers who may/may not have been motivated to quit. Participants using nicotine e-cigarettes were more likely to quit smoking compared with those using placebo e-cigarettes (RR=2.29, 95% CI 1.05-4.96, p= 0.037). Among 657 participants who were current smokers (>10 cigs/day) and who wanted to quit smoking, persons randomized to an e-cigarette group had reduced their mean daily tobacco use significantly more compared with persons in the nicotine patch group or the placebo e-cigarette group (1.9 vs 9.7 vs. 7.7 cigs/day, p=0.002); however, the superiority of nicotine e-cigarettes over nicotine patches or placebo e-cigarettes could not be established due to lower than expected quit rates (10% was anticipated)(Bullen et al. 2013). Nevertheless, the safety of e-cigarettes remains unclear. There is evidence that the use of e-cigarette devices may expose the user to substances which may increase vascular inflammation and cause the development of pulmonary changes.

Birth Control/Hormone Replacement Therapy

Women taking oral contraceptive or hormone replacement therapy (HRT) may be at an increased risk of stroke. In a Cochrane review (Roach et al. 2015) that included the results of 24 studies, combined oral contraception users were found to be at increased risk of MI or ischemic stroke (RR=1.6, 95% CI 1.3-1.9), MI (RR=1.6, 95% CI 1.2 to 2.1) and ischemic stroke (RR=1.7, 95% CI 1.5 to 1.9) compared with non-users. The risk of both events increased with increasing doses of estrogen. In a large cohort study including the results of over 1.6 million women between the ages of 15 and 49 years, Lidegaard et al. (2012) reported that current use of ethinyl estradiol at doses of 20 to 50 µg was associated with an increased risk of thrombotic stroke, compared with nonusers, while current use of progestin only was not.

Hormone replacement therapy was not found to significantly increase the risks of all-cause mortality, nonfatal MI, angina or need for revascularization when used for primary or secondary CVD prevention in a Cochrane review (Boardman et al. 2015); however, the risk of stroke was increased significantly (RR=1.24, 95% CI 1.10 to 1.4), as were the risks of venous thromboembolism and PE (RR=1.92, 95% CI 1.36 to 2.69 and RR=1.81, 95% CI 1.32 to 2.48, respectively). Similarly, Renoux et al. (2010) reported that, compared to non-users, women using oral HRT within the previous year had a higher risk of stroke (RR= 1.28, 1.15-1.42). Use of oral HRT for >1 year was associated with increased risk of stroke (RR=1.35, 95% CI 1.20-1.52), but not for a duration of ≤1 year. High dose transdermal patch use was associated with an increased risk of stroke (RR=1.89, 95% CI 1.15-3.11), although low- dose patches were not (RR=0.95, 0.75-1.20). The risk of stroke was also significantly increased in the Women's Health Initiative, among women in the combined estrogen/progesterone group compared with placebo (HR=1.31, 95% CI 1.02-1.68).

Compliance with Secondary Prevention Measures

Since rates of recurrent stroke, and other vascular disorders are known to be significantly elevated during the first four years after hospitalization for first stroke (Feng et al. 2010), and potentially modifiable risk factors represent approximately 90% of the population-attributable risk for stroke (O'Donnell et al. 2016), secondary prevention measures represent an important opportunity to reduce the risk. While the effectiveness of many of the interventions designed to prevent recurrent stroke,

including medications associated with hypertension, diabetes, dyslipidemia and cardiac conditions (described in other sections of the guidelines) are well-established, their protective effects are diminished by poor compliance. Efforts aimed at improving compliance through behavioral or educations interventions have been disappointing in several recent RCTs. Fukuoka et al. (2019) reported no difference between groups in mean Framingham risk score after a 6-month nurse-led disease management program (DMP) or usual care. A Cochrane review (Bridgwood et al. 2018), which included the results from 42 trials examining interventions to improve modifiable stroke risk factors, also reported no differences in blood pressure, serum cholesterol, HbA1c or BMI between intervention and usual care groups at the end of treatment.

Emerging Risk Factors

i) Influenza

Seasonal influenza has been shown to increase the risk of stroke and heart disease (Kwong et al. 2018, Boehme et al. 2018). In a case-crossover study involving 36,975 patients hospitalized for ischemic stroke, the odds of stroke were increased by 288% given prior influenza exposure within the previous 15 days, decreasing to 168% given exposure within the previous 60 days. The risk was highest among persons aged 18-45-years with influenza exposure within the previous 15 days (OR= 9.28, 95% CI 1.72–50.2). Field et al. (2004) examined data from hospital stroke admissions in a large Canadian city from 1994-2001, and reported that during that period, as influenza rates increased, so did stroke rates. The slope of the β co-efficient for total stroke was 0.63 (95% CI 0.58-0.67).

The influenza vaccine can reduce the added risk of stroke. Tsivgoulis et al. (2018) reported the risk of ischemic stroke was reduced significantly among persons who received influenza vaccine, a portion of whom had a previous stroke (RR=0.87, 95% CI 0.79-0.96, p=0.004). Lee et al. (2017) also reported the overall risk of stroke was reduced significantly in vaccinated persons (OR= 0.82; 95% CI 0.75–0.91; p < 0.001). Decreased risks of cardiovascular events and deaths associated with influenza vaccination has been reported elsewhere (Clar et al, 2015, Udell et al. 2013).

ii) Air Pollution

Pollutants such as particulate matter (PM), ozone, sulphur dioxide, carbon monoxide, nitrogen dioxide, and nitrogen oxide, represent a significant risk to health. For example, long-term exposure to PM with an aerodynamic diameter of ≤ 2.5 μm ($PM_{2·5}$) contributed to 4.2 million deaths and to a loss of 103.1 million disability-adjusted life years (DALYs) in 2015, representing 7.6% of total global deaths and 4.2% of global DALYs (Cohen et al. 2017). However, in 2015, data from the same study revealed that Canada was among the countries with the lowest exposure to $PM_{2·5}$ with concentrations ≤8·0 μg/m³. A recent systematic review (Yang et al. 2019), included the results from 35 studies, of which 17 were from the USA and 6 were from Canada. Each 10 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with a significantly increased risk of stroke (RR=1.12, 95% CI 1.02–1.16), and stroke mortality (RR=1.11, 95% CI 1.07–1.14). Data from 2,145,400 persons included in the 1991-2001 Canadian mortality follow-up study indicated the risks of mortality associated with long-term exposure to $PM_{2.5}$ significantly increased the risks of cardiovascular diseases, circulatory diseases, and ischemic heart disease, while the risk of mortality-related cerebrovascular disease, was not (Crouse et al. 2012).

Evidence Table and Reference List 2a: Lifestyle & Risk Factor Management (Healthy Balanced Diet)
Evidence Table and Reference List 2b: Lifestyle & Risk Factor Management (Alcohol Consumption, Recreational Drug Use and Smoking Cessation)
Evidence Table and Reference List 2c: Lifestyle & Risk Factor Management (Physical Activity, Weight Management, Oral Contraceptives, Hormone Replacement Therapy, Air Pollution, Behaviour Management)
Evidence Table and Reference List 2d: Lifestyle & Risk Factor Management (Influenza Infection, Vaccination & Stroke Risk)

3.0 Blood Pressure and Stroke Prevention

Section 3 Recommendations 2020

Note: These recommendations are applicable to transient ischemic attack, and stroke of ischemic and hemorrhagic origin unless otherwise stated, for secondary prevention.

3.0 Blood pressure should be assessed and managed in all persons with stroke or transient ischemic attack [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. *Hyperlink to current Hypertension Canada Guidelines and Protocols for Blood Pressure Measurement (http://guidelines.hypertension.ca/).*

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]. *Refer to recommendations in Section 2 on Lifestyle Behaviour and Management for additional information, including sodium and diet management.*

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 transient ischemic attack [Evidence Level A].

ii. For patients **who have had an ischemic stroke or transient ischemic attack**, 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 transient ischemic attack. Blood pressure lowering treatment should be initiated or modified before discharge from hospital [Evidence Level B]. *Refer to Hyperacute Module Recommendations Section 3.3 for blood pressure management during the acute phase of stroke (0 – 72 hours).*

vii. Treatment with an 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 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*

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.

Rationale

Elevated blood pressure is the single most important risk factor for stroke. One in five adult Canadians has blood pressure in the range of 130–139/85–89 mm Hg (labeled by some investigators as “pre-hypertension”), and up to 60 percent of them will develop hypertension within four years. Among persons aged 55 and older with normal blood pressure, 90 percent will develop hypertension if they live to an average age. All adults require ongoing assessment of blood pressure throughout their lives. Each 1 mm Hg increase in blood pressure increases the risk of poor late-life cognitive function by approximately one percent. Epidemiologic studies have shown a graded increase in the risk of stroke as blood pressure increases.

Numerous population-based studies have found that elevated blood pressure is a significant risk factor for first and recurrent stroke; hypertension is estimated to account for about 60 percent of the population-attributable risk for cerebrovascular disease. The InterStroke study reported an odds ratio of 2.64 for patients with hypertension experiencing a stroke. Several trials have shown a 28 percent risk reduction in recurrent stroke in patients treated with blood pressure lowering medication. Among persons with a previous stroke the risk of recurrent stroke was reduced significantly with intensive antihypertensive therapy, with an NNT of 67. (Kitagawa et al. 2019)

The optimal target for blood pressure in people who have had a stroke and people at risk of stroke has not been formally defined through randomized controlled trials. The current treatment recommendation is to attain a blood pressure of consistently lower than 140/90 mm Hg for people who have had a cerebrovascular event. Epidemiologic data have shown that those with a response to treatment

attaining blood pressure levels well below 140 systolic and 90 diastolic have better outcomes yet these treatment trials have not yet clearly defined how far blood pressure should be lowered.

People who have experienced a stroke have reported lack of awareness or attention to blood pressure readings prior to their stroke. They emphasize that education on blood pressure management is an essential part of care, yet they also reflect that the magnitude of impact of elevated blood pressure on secondary stroke risk was not made clear to them. Stroke teams and other care providers have opportunities to improve awareness and management of blood pressure and equip people who have experienced a stroke with the knowledge, measurement, and tracking/recording tools they need to mitigate future risk.

System Implications

1. Coordinated hypertension awareness programs at the provincial and community levels that involve community groups, primary care providers (physicians, nurse practitioners and pharmacists) and other relevant partners.
2. Stroke prevention, including routine blood pressure monitoring, offered by primary care providers in the community as part of comprehensive patient management.
3. Increased availability and access to education programs about hypertension diagnosis and management for adults and children for healthcare providers across the continuum of care.
4. Increased support for home blood pressure monitors (e.g., programs or tax credits) for patients and families on home monitoring of blood pressure and blood pressure self-management programs.
5. Universal and equitable access to cost-effective medicines for all people in Canada, regardless of geography, age, or ability to pay.

Performance Measures

1. Proportion of persons at risk for stroke who had their blood pressure measured at their last healthcare encounter; and within the last 12 months.
2. Proportion of the population who have diagnosed elevated blood pressure (hypertension).
3. Proportion of the population who are aware of hypertension and the risks of high blood pressure.
4. Percentage of the population with known hypertension who are on blood pressure lowering therapy.
5. Proportion of the population with hypertension who are being treated and have achieved control of their blood pressure within defined targets (as per Canadian Hypertension Education Program guidelines) though lifestyle changes and/or medication.
6. Proportion of stroke and transient ischemic attack patients who have received a prescription for blood pressure lowering agents on discharge from acute care.
7. Proportion of stroke and transient ischemic attack patients who have received a prescription for blood pressure lowering agents after assessment in a secondary prevention clinic.

Measurement Notes

1. Performance measures 1 through 3: data may be available through the Canadian Hypertension Education Program database, the Canadian Community Health Survey, and other provincial and local health surveys and patient self-reports.
2. Performance measures 4: data may be available through audit of primary care provider's charts. Prescription information may also be available through provincial drug plan databases, although these may have limitations with respect to the age of those covered by the plans, and there is variation across provinces and territories.

3. Performance measures 7: prescriptions for blood pressure lowering agents may be given during the inpatient stay or during a secondary prevention assessment and follow- up. When tracking these performance rates, it is important to record the setting where this therapy is initiated. Data sources may include patient/medical order sheets, physicians' or nurses' notes, discharge summaries or copies of prescriptions given to patients.
4. Prescriptions given to a patient do not imply compliance.
5. Algorithms to identify incidence and prevalence of hypertension from administrative databases have been validated in Canada and should be used for consistency in measurement when possible.[104]

Implementation Resources and Knowledge Transfer Tools

Health Care Provider Information

- Heart & Stroke Blood Pressure Resources: https://www.heartandstroke.ca/heart-disease/risk-and-prevention/condition-risk-factors/high-blood-pressure
- Heart & Stroke: Post-Stroke Checklist: https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/002-17_csbp_post_stroke_checklist_85x11_en_v1
- Hypertension Canada guidelines: https://guidelines.hypertension.ca/chep-resources/
- Canadian Task Force on Preventive Health Care for primary prevention screening guidelines for hypertension: https://canadiantaskforce.ca/guidelines/published-guidelines/hypertension/

Patient Information

- Heart & Stroke: Post-Stroke Checklist: https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/002-17_csbp_post_stroke_checklist_85x11_en_v1
- Heart & Stroke: Your Stroke Journey: https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/en-your-stroke-journey-v21
- Heart & Stroke: Online and Peer Support https://www.heartandstroke.ca/heart-disease/recovery-and-support/the-power-of-community
- Heart & Stroke: Blood Pressure Resources: https://www.heartandstroke.ca/heart-disease/risk-and-prevention/condition-risk-factors/high-blood-pressure
- Heart & Stroke: Managing your blood pressure: https://www.heartandstroke.ca/-/media/pdf-files/canada/health-information-catalogue/en-managing-your-blood-pressure
- Heart & Stroke: Blood pressure wallet card: https://www.heartandstroke.ca/-/media/pdf-files/canada/other/en-blood-pressure-wallet-card-v3-web
- Heart & Stroke: Resource on DASH diet: https://www.heartandstroke.ca/healthy-living/healthy-eating/dash-diet
- Heart & Stroke: Working with your doctor: www.heartandstroke.ca/heart-disease/recovery-and-support/working-with-your-doctor

- Heart & Stroke: Stroke medications resource: https://www.heartandstroke.ca/stroke/treatments/medications
- Canadian Hypertension Resources: https://hypertension.ca/hypertension-and-you/ including:
  Hypertension: What you need to know – About Hypertension & Managing Hypertension
  Hypertension: What can I do?
  Blood Pressure Log - consistently measure and record your blood pressure with this log
  Blood Pressure Action Plan - guidance on creating an action plan to keep your blood pressure in the healthy range

Summary of the Evidence 2020

Stroke Risk and Hypertension

Hypertension is widely regarded as the most important modifiable risk factor for stroke. Results from phases 1 and 2 of the INTERSTROKE study (O'Donnell et al. 2010, O'Donnell et al. 2016), indicated that among the five risk factors that accounted for more than 80% of the risk for stroke, hypertension was found to be most significant. The others included current smoking, abdominal obesity, diet, and physical activity. In phase 1 of the study, a self-reported history of hypertension or measured blood pressure ≥160/90 mm Hg was associated with an increased risk of all stroke (OR=2.98, 99% CI 2.72-3.28), but was highest for hemorrhagic stroke (OR=9.18, 99% CI 6.80-12.39). The same risk pattern was reported in phase 2 of the study, which used a self-reported history of hypertension or measured blood pressure ≥140/90 mm Hg to define hypertension (O'Donnell et al. 2016). The risk of hemorrhagic stroke was significantly increased (OR=4.09, 99% CI 3.51-4.77). In another case-control study, Du et al. (2000) reported the risk of stroke was significantly higher among subjects who were hypertensive (OR=2.45, 95% CI 1.62 to 3.71, p< 0.001) and the risk of stroke increased with additional risk factors including smoking and diabetes. The authors suggested that at least three-quarters of strokes in hypertensive patients are preventable given appropriate treatment. The authors further emphasized that strokes are caused not by a single risk factor, but by the interaction of multiple risk factors, with some having a stronger independent relationship with stroke than others. A meta-analysis (Lewington et al. 2002) that included the results of one million adults from 61 prospective studies found that an increase of 20 mm Hg in systolic and 10 mm Hg in diastolic blood pressure led to a two-fold increase in stroke mortality in persons aged 40 – 69 years, without any evidence of a threshold down to at least 115/75 mm Hg for all vascular deaths. Age-specific associations were found to be similar for men and women, and for cerebral hemorrhage and cerebral ischemia. Data from 1.25 million people without a history of cardiovascular disease, included in the CALIBER database were used to estimate lifetime risks and years of life lost to cardiovascular disease (Rapsomanki et al. 2014). During a median follow-up of 5.2 years, for each 20/10 mm Hg increase, the risks of transient ischemic attack, ischemic stroke and ICH increased across age cohorts (30-59, 60-79 and ≥80 years), with the highest risks noted in the youngest patients. The lifetime risk of ischemic stroke (from index age of 30 years) in persons with hypertension, defined as ≥140/90 mm Hg, was 7.6% (95% CI 7.3%-7.8%) compared with 6.5% (95% CI 6.2%-6.9%) for persons without hypertension. The years of life lost to ischemic stroke for those with hypertension was approximately a half a year.

Pharmacological Treatment of Hypertension Reduces Stroke Risk

Among persons who sustained an acute stroke, antihypertensive treatment, initiated within 48 hours of the event was shown to significantly reduce the risk of recurrent stroke at >12 months, compared with placebo or no treatment (RR=0.81, 95% CI 0.70-0.93). The effect was most pronounced for persons with baseline SBP>140 mm Hg. ACE inhibitors and diuretics were found to be the most effective antihypertensive agents (Zonneveld et al. 2018). The risks of recurrent stroke, disabling or fatal stroke and cardiovascular death were all significantly reduced following antihypertensive treatment compared with placebo in a systematic review including 14 RCTs (Katsanos et al. 2017). In meta-regression analysis, increasingly lower SBP was linearly associated with significant reductions in recurrent stroke, MI, death from any cause and cardiovascular death. Several meta-analyses included trials with

persons both with and without previous stroke. Intensive blood pressure treatment was shown to decrease the risk of recurrent stroke compared with less intensive treatment by 22% (HR=0·78, 95% CI 0·67–0·90, p=0·001), after a mean duration of follow-up of 3.8 years (Xie et al. 2016, n=19 trials). Bangalore et al. (2017) included trials comparing different goal systolic blood pressure (SBP) targets (<150, <140, <130 and <120 mm Hg) against a reference standard of <160 mm Hg. The risk of stroke was decreased in a comparison of target SBP <120 vs. <160 mm Hg, the reference standard (RR=0.54, 95% CI 0.29-1.00), but there were no significant reductions in risk for any of the other pairings (<150 vs. <160 mm Hg; <140 vs. <160 mm Hg; <130 vs. <160 mm Hg). Looking from a different perspective, compared with a target SBP of <120 mm Hg, the risk of stroke was significantly increased with SBP <140 mm Hg (RR=1.72, 95% CI 1.42-2.58), <150 mm Hg (RR=1.97, 95% CI 1.26-3.08) and <160 mm Hg (RR=3.27, 95% CI 1.78-6.00). The authors suggested that SBP targets of <120 and <130 mm Hg were best for stroke prevention. Ettehad et al. (2016) included the results of 123 RCTs examining persons with and without previous stroke or transient ischemic attack. The risk of major cardiovascular events was reduced significantly for each 10 mm Hg reduction in SBP (RR= 0·80, 95% CI 0·77–0·83), including stroke (RR=0·73, 95% CI 0·68–0·77), with the magnitude of risk reduction proportional to the blood pressure reduction achieved. The risk of stroke was reduced significantly per each 10 mm Hg decrease in SBP with antihypertensive treatment in persons with and without existing cardiovascular disease (RR=0·74, 95% CI 0.67-0.81 and RR=0·75, 95% CI 0.63-0.89, respectively). The most effective antihypertensive agents for the reduction in stroke risk were angiotensin receptor blockers and calcium channel blockers. Beta-blockers were inferior to other classes of antihypertensives. The risk of stroke was reduced with antihypertensive treatment across different 10 mm Hg strata of baseline SBP ≥130. Lee et al. (2012) included the results of 11 RCTs representing data from 42,572 participants (794 with previous stroke) who were at high risk for cardiovascular disease and compared treatment of tight blood pressure control (SBP <130 mm Hg) with usual control (SBP 130 to 139 mm Hg) on subsequent stroke risk. Tight SBP target was associated with reduced risks of future stroke, and major vascular events, and major coronary events, but was not associated with a significantly lower risk of death. Among patients with diabetes, those without a history of CVD, and younger than 65 years experienced the greatest stroke risk reduction.

A recent clinical trial (RESPECT) compared standard blood pressure treatment, with a target of <140/90mm Hg, with intensive treatment target of <120/80 mm Hg, among 1,280 patients with a stroke sustained within the previous 30 days to 3 years with a baseline SBP of 130 to 180 mm Hg or DBP of 80 to 110 mm Hg. Unfortunately, the trial was stopped prematurely, before planned recruitment of 2,000 participants (Kitagawa et al. 2019). After a mean duration of follow-up of 3.8 years, there were 52 strokes (2.26% per year) in the standard group and 39 (1.65% per year) in the intensive group. The risk of recurrent stroke was not reduced significantly with intensive BP treatment (HR=0.73, 95% CI 0.49-1.11, p=0.15). The Secondary Prevention of Small Subcortical Strokes (SPS3 Trial) examined the effectiveness of medical management to reduce recurrent stroke in persons with a lacunar stroke, sustained within the previous 180 days. Lowering systolic blood pressure (SBP) to a target of < 130 mm Hg resulted in a non-significant reduction on all stroke, disabling stroke, myocardial infarction and vascular death compared with target SBP levels of 130-149 mm Hg (Benavente et al. 2013).

Lower blood pressure targets (<130/80 mm Hg) have been recommended for persons with diabetes for the prevention of first or recurrent stroke. A Cochrane review (Arguedas et al. 2013) included the results from 5 RCTs comparing 'lower' blood pressure targets (any target <130/85mm Hg) with 'standard' targets (<140-160/90-100 mm Hg). Participants were adults with type 2 diabetes and elevated blood pressure, or already receiving treatment for elevated blood pressure. In the single included trial, which aimed at reductions in systolic blood pressure (ACCORD 2010) intensive BP control was not associated with reductions in total mortality (RR= 1.05, 95% CI 0.84-1.30) but was associated with reduction in the risk of stroke (RR=0.58, 95% CI 0.39 to 0.88, p= 0.009); however, serious adverse events, attributed to therapy occurred more often in patients in the intensive group (3.3% vs. 1.3%, p<0.001). In the 4 trials aimed at reductions in diastolic blood pressure, intensive BP control was not associated with reductions in total mortality (RR= 0.73, 95% CI 0.53-1.01, p=0.054) or stroke (RR= 0.67, 95% CI 0.42-1.05, p=0.077). In the UKPDS (Turner et al. 1988), the risk of fatal and nonfatal stroke (combined) was reduced by 44% (HR= RR=0.56, 95% CI 0.35-0.89, p=0.013) among patients in the tight BP control (mean BP achieved 144/82 mm Hg) compared with less aggressive

control (mean BP achieved 154/87 mm Hg).

Sex and Gender Considerations

The evidence is conflicting regarding the increased risk of ischemic stroke associated with hypertension according to sex. There was no indication to suggest a sex difference in the relationship between systolic blood pressure (SBP) and the risk of stroke in a large meta-analysis including 124 studies (Peters et al. 2013) or from the CALIBER study including over 1.25 million persons (Rapsomaniki et al. 2014). In one of the REGARDS publications (Madsen et al. 2019), which included data from 26,461 participants, the risk of stroke was increased significantly more per each 10 mm Hg increase in SBP in women (HR=1.15, 95% CI, 1.10–1.20 vs. HR=1.08, 95% CI, 1.03–1.14, p for interaction=0.09).

Control of hypertension was found to be significantly higher among women <60 years compared with men (56.3% vs. 50.6%); but was lower among women aged ≥60 years (50.8% for women vs. 54.6% for men, p<0.05) (Yoon et al. 2015). Although not statistically significant, intensive blood pressure lowering was found to reduce the risk of major cardiovascular events, including stroke, more in men compared with women in a sub analysis of the SPRINT trial (HR=0.84, 95% CI 0.61–1.13 vs. HR=0.73, 95% CI 0.59–0.89, p value for interaction=0.45) (Foy et al. 2018).

Blood Pressure and Stroke Prevention Evidence Tables and Reference List

4.0 Lipid Management

Note: For detailed management of dyslipidemia, refer to current Canadian Cardiovascular Society guidelines on this topic. www.ccs.ca/guidelines

Section 4 Recommendations 2020

4.0 Individuals who have had an ischemic stroke or transient ischemic attack 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 transient ischemic attack [Evidence Level B]. *Refer to Table 1A for more information on laboratory tests.*

4.2 Lipid Management

i. Individuals with ischemic stroke or transient ischemic attack 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]. *Refer to Prevention of Stroke Module, Section 2 for Lifestyle Management recommendations.*

ii. Statin pharmacotherapy should be prescribed for secondary prevention of stroke in individuals who have had a non-cardioembolic ischemic stroke or transient ischemic attack, [Evidence Level A]. *Refer to the current Canadian Cardiovascular Society Dyslipidemia guidelines for additional information on lipid management.*

   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]. *Refer to CSBPR Management of Intracerebral Hemorrhage module for additional information on stroke prevention strategies in that population.*

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 where 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 [Level of Evidence 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]

*Note: For diagnosis and management of dyslipidemia in the **primary prevention** of cardiovascular events, including stroke, refer to the current Canadian Cardiovascular Society Dyslipidemia guidelines.*

Rationale

High cholesterol and lipids in the blood are associated with a higher risk of vascular events including stroke and myocardial infarction. People who have already had an ischemic stroke or transient ischemic attack will benefit from cholesterol-lowering medications with a statin class of drug. Aggressive reduction of low-density lipoprotein cholesterol is likely to yield greater benefit than more modest reductions. A 16 to 30 percent relative risk reduction has been reported in recurrent vascular events for patients with a history of stroke without coronary artery disease who are treated with statin agents.

The Cholesterol Treatment Trialists meta-analysis of 14 statin trials showed a dose-dependent relative reduction in cardiovascular disease with low-density lipoprotein cholesterol lowering. Every 1.0 mmol/L reduction in low-density lipoprotein cholesterol is associated with a corresponding 20 to 25 percent reduction in cardiovascular disease mortality and nonfatal myocardial infarction with and NNT of 30 reported by the Treat to Target trial (2020).

People who have experienced stroke report a wide range of approaches to the way their lipids are managed; some are referred to and followed by a lipid specialist and others by their family doctor, whereas others have reported never had their lipids discussed (SPoS CCRP, 2019). An individualized approach to lipid management is necessary to help people be successful in reaching their appropriate lipid targets. Our Community Review Panel emphasize the importance of a comprehensive approach to lipid management that includes education on medications, diet, exercise, weight management and clear information on what their target lipid level should be, their prescribed medication regime, and potential side effects and how the side effects can be managed.

Note: The current clinical trial evidence does not include enough stroke patients with atrial fibrillation or other cardioembolic sources to make specific recommendations for this patient population. The decision to use statins in this setting should be based on the patient's global cardiovascular risk. It is unclear whether statins are of benefit in patients with a combination of atrial fibrillation and stroke.

System Implications

1. Coordinated dyslipidemia awareness programs at the provincial and community levels that involve community groups, primary care providers (including physicians, nurse practitioners and pharmacists), and other relevant partners.
2. Stroke prevention, including lipid level monitoring and education, offered by primary care providers in the community as part of comprehensive patient management.
3. Increased availability and access to education programs on dyslipidemia diagnosis and management for healthcare providers across the continuum of care.
4. Continued alignment with recommendations and guidelines developed by the Canadian Cardiovascular Society Dyslipidemia group.
5. Universal and equitable access to cost-effective medicines for all people in Canada, regardless of geography, age, or ability to pay.

Performance Measures

1. Proportion of stroke patients who have lipid levels completed as part of initial comprehensive assessment.
2. Proportion of the population who report that they have elevated lipid levels, especially low-density lipoprotein.
3. Proportion of stroke patients prescribed lipid-lowering agents for secondary prevention of stroke, either at discharge from acute care, through a secondary prevention clinic or by primary care provider (includes MD and NP).

Measurement Notes

1. Performance measures 1 and 2: Data may be available through the Canadian Community Health Survey.
2. Performance measure 2: Blood values should be taken from official laboratory reports where possible.
3. Performance measure 3: Data sources may include physician order sheets, physicians' and nurses' notes, discharge summaries, or copies of prescriptions given to patients.
4. Prescriptions for lipid-lowering agents may be given during the inpatient stay or during a secondary prevention assessment and follow-up, either in a stroke prevention clinic or in a primary care setting. When tracking these performance rates, it is important to record the setting where this therapy was initiated.
5. Prescriptions given to a patient do not imply compliance.

Implementation Resources and Knowledge Transfer Tools

Health Care Provider Information

- Heart & Stroke: Post-Stroke Checklist: https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/002-17_csbp_post_stroke_checklist_85x11_en_v1
- CSBPR: Management of Spontaneous Intracerebral Hemorrhage, Secondary Stroke Prevention in and Individual with Intracerebral Hemorrhage https://www.strokebestpractices.ca/recommendations/management-of-intracerebral-hemorrhage
- Canadian Cardiovascular Society Dyslipidemia Recommendations: https://www.ccs.ca/en/guidelines/guidelines-library
- Framingham Cardiovascular Risk Calculator: https://www.framinghamheartstudy.org/fhs-risk-functions/cardiovascular-disease-10-year-risk/
- National Heart, Lung and Blood Institute Patient Educational Materials: https://www.nhlbi.nih.gov/health-pro/resources

Information for People with Stroke, their Families and Caregivers

- Heart & Stroke: Post-Stroke Checklist: https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/002-17_csbp_post_stroke_checklist_85x11_en_v1
- Heart & Stroke: Your Stroke Journey: https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/en-your-stroke-journey-v21
- Heart & Stroke: Online and Peer Support https://www.heartandstroke.ca/heart-disease/recovery-and-support/the-power-of-community
- Heart & Stroke: Managing Cholesterol:

https://www.heartandstroke.ca/heart/risk-and-prevention/condition-risk-factors/high-cholesterol

- Heart & Stroke: How to manage your cholesterol: https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/hs-f20-cholesterol-brochure-en-v3
- Cholesterol lowering medications: https://www.heartandstroke.ca/heart/treatments/medications/statins
- AHA resources: https://www.heart.org/en/health-topics/cholesterol/cholesterol-tools-and-resources

Summary of the Evidence 2020

Given the well-documented causal relationship between dyslipidemia and the development of atherosclerosis, appropriate management is important for both primary and secondary prevention of stroke. To maximize treatment and improve outcomes for cardiovascular disease, current strategies emphasize the need to balance lifestyle and risk factor modifications through behaviors change with pharmacological intervention.

Evidence from several systematic reviews has demonstrated a significant reduction in overall risk of ischemic stroke and other vascular events associated with lipid-lowering therapies. In one of the more recent Cholesterol Treatment Trialists (CTT) publications (Fulcher et al. 2015), 27 RCTS (n=186,854) were included, in which the treatment aim was solely the reduction of LDL cholesterol and was continued for at least two years. Treatment contrasts included statin vs. placebo and more intensive vs. less intensive treatment. After a median duration of follow-up of 4.9 years, overall, statins reduced the risk of a major vascular event by 21% per each 1.0 mmol/L reduction in LDL-chol (RR=0.79, 95% CI 0.77-0.81), with no significant interaction reported for sex. The risks of any stroke and any vascular death were also decreased significantly with statin therapy (RR=0.85, 95% CI 0.80-0.89, and RR=0·88, 95% CI 0·84−0·91, respectively), again with no significant interaction based on sex. Statins significantly reduced the risk of a major vascular event and vascular death across all age groups from ages ≤55 to >75 years, per each 1.0 mmol reduction in LDL-chol (Armitage et al. 2019). Lipid-lowering treatment was associated with a significant decrease in stroke risk among persons with a >5% to 30%, 5-year risk of stroke (Mihaylova et al. 2012).

The results of many primary prevention trials including participants with cerebrovascular risk factors have demonstrated the effectiveness of statin therapy. Although too many to describe in detail, we present the results of just a few that compared varying doses of statins with placebo, which included persons with differing levels of cardiovascular risk. The Heart Protection Study (2002) randomized 20,536 patients with coronary artery disease, cerebrovascular disease, peripheral vascular disease, diabetes or patients over 65 years with hypertension and a total serum cholesterol of > 3.4 mmol/L to receive 40 mg simvastatin or placebo for a mean duration of five years. There was a significant reduction in ischemic stroke associated with statin therapy (RRR=25%, 95% CI 15%– 44). In addition, patients in the simvastatin arm required fewer carotid endarterectomies and angioplasties. These benefits were evident across all subgroup, even those whose baseline LDL cholesterol was under 2.6 mmol/L, suggesting the decision to initiate statin therapy should include an assessment of a patient's absolute risk of cardiovascular disease, rather than just their LDL cholesterol concentration. A statin dose of 20 mg/day was used in the Justification for the Use of Statins in Prevention Trial Evaluating Rosuvastatin (JUPITER) trial (Ridker et al. 2008). This trial, which was terminated early (median of 1.9 years), included 17,802 men (≥50 years) and women (≥60 years) without a history of cardiovascular disease, with a normal LDL-chol level, but with elevated C-reactive protein levels of ≥2.0mg/L. Study participants were randomized to receive 20 mg/day rosuvastatin or placebo. There were significantly

more strokes (any and nonfatal) (64 vs. 33 and 58 vs. 30, respectively). The associated hazard ratios were 0.52, 95% CI 0.34-0.79, p=0.002 and 0.52, 95% CI 0.33-0.80, p=0.003. Most recently, in the satin arm blood-pressure lowering arm of the Heart Outcomes Prevention Evaluation (HOPE)-3 trial, (Yusuf et al. 2016), patients at intermediate risk of cardiovascular disease (i.e., those without a history of CVD but with at least one or two risk factors, depending on age) were randomized to treatment with 10 mg/day rosuvastatin or placebo. At the end of follow-up (median of 5.6 years), the mean LDL-chol and apoprotein B-100 were significantly lower in the statin group by 26.5% and 22.0%, respectively. The risk of the first primary outcome, which included nonfatal stroke was significantly lower in the statin group (3.7% vs. 4.8%, HR=0.76, 95% CI 0.64-0.91, p=0.02). The risk of any stroke was also significantly lower in the statin group (1.1% vs. 1.6%, HR=0.70, 95% CI 0.52-0.95).

There has only been one large RCT evaluating statin monotherapy for secondary prevention of stroke (Amarenco et al. 2006). The Stroke Prevention by Aggressive Reduction in Cholesterol Levels trial (SPARCL) included 4,731 patients with previous stroke or transient ischemic attack within one to six months before study entry, who had LDL levels of 2.6 to 4.9 mmol/L and had no known coronary artery disease. Participants were randomized to receive treatment with atorvastatin 80 mg once daily or placebo. The mean LDL level during the trial was 1.9 mmol/L among patients receiving atorvastatin versus 3.3 mmol/L in the placebo group. The 5-year absolute reduction in risk of any stroke was 2.2 percent; with a relative risk reduction of 16%, and adjusted hazard ratio (HR) 0.84 (95% CI 0.71–0.99; p = 0.03). Based on this data, 46 patients would need to be treated for 5 years to prevent one stroke. The authors cautioned that the reduction in ischemic stroke (HR=0.78, 95% CI 0.66–0.94) should be weighed against the increased risk of hemorrhagic stroke (HR=1.66, 95% CI 1.08- 2.55). The five-year absolute reduction in risk of major cardiovascular events was 3.5 percent (HR=0.80, 95% CI 0.69–0.92; p = 0.002). More recently, the link between statin use and increased risk of intracerebral hemorrhage has been questioned. Using results from the VISTA archive, Scheitz et al. (2016), reported no increased risk of intracerebral hemorrhage following ischemic stroke in patients who were established previously on statin therapy or in those who were newly initiated on it.

When added to background statin therapy, the use of additional agents including, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, a monoclonal antibody; ezetimbe, a cholesterol absorption inhibitor; and icosapent ethyl, a highly purified eicosapentaenoic acid ethyl ester, have been shown to be effective in further reducing vascular events in persons whose cholesterol and/or triglycerides, remain high on statin monotherapy, or in those who have had a further event. New recommendations have been made regarding the use of these agents in this update of the Canadian Stroke Best Practice Recommendations.

In persons with established atherosclerotic cardiovascular disease, the combination of 10 mg ezetimibe and 40 mg of simvastatin was found to be superior to monotherapy with simvastatin for reduction of the risk of vascular outcomes, including stroke (Cannon et al. 2015). The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) included 18,144 patients recently hospitalized with acute coronary syndrome with elevated LDL cholesterol. The risk of the primary outcome (a composite of fatal and nonfatal cardiovascular events) over 7 years was significantly lower in the dual-therapy group (32.7% vs. 34.7%; HR=0.936, 95% CI 0.89-0.99, p=0.016). The risks of any stroke and ischemic stroke were significantly lower in the dual therapy group (HR=0.86, 95% CI 0.73-1.00, p=0.05 and HR=0.79, 95% CI 0.67-0.94, p=0.008, respectively), while the risk of hemorrhagic stroke was not reduced significantly. The use of ezetimibe to achieve further reductions in LDL cholesterol may help to protect against recurrent cardiovascular/cerebrovascular events. The *Treat Stroke to Target trial (*Amarenco et al. 2020) randomized 2,860 participants who had sustained an

ischemic stroke in the previous 3 months or a transient ischemic attack within the previous 15 days, who had confirmed atherosclerotic disease, to receive treatment with either a statin or a statin + ezetimibe, if required, to achieve a target LDL cholesterol level of < 1.8 mmol/L, (lower-target group) or a target range of 2.3 to 2.8 mmol/L, (higher-target group), for the duration of the trial. At the end of follow-up (mean 3.5 years), the mean LDL cholesterol was 1.7 mmol/L in the lower-target group and 2.5 mmo/L in the higher-target group. The risk of major cardiovascular events, the primary outcome, was significantly lower in the lower-target group (8.5% vs. 10.9%, HR=0.78, 95% CI 0.61 to 0.98; p=0.04).

PCSK9 inhibitors have also been shown to reduce the risk of cardiovascular events, in addition to statin therapy. 19,924 persons with elevated LDL cholesterol and a hospitalization for an acute coronary syndrome who received 75 mg alirocumab subcutaneously every 2 weeks, in addition to maximum statin therapy, for an average of 2.8 years, had a 15% reduced risk of the primary outcome (a composite of death from coronary heart disease, nonfatal MI, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization) compared with persons taking a statin only in the ODYSSEY OUTCOMES Trial (Schwartz et al. 2018). In the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) Trial (Sabatine et al. 2017), 27,564 patients from 49 countries, with established atherosclerotic cardiovascular disease and a fasting LDL cholesterol level of ≥1.8 mmol/L, or HDL chol level of ≥2.6 mmol/L, who were already receiving ≥20 mg/day of a statin were randomized receive evolocumab (140 mg every 2 weeks or 420 mg every month, by subcutaneous injection) or placebo. At 48 weeks, the mean absolute reduction in serum LDL-cholesterol associated with evolocumab was 1.45 mmol/L. The risk of the primary outcome (a composite of cardiovascular events including stroke) was significantly lower for patients in the evolocumab group (9.8% vs. 11.3%, HR=0.85, 95% CI 0.79–0.92, p<0.001). The risk of any stroke was also significantly lower for patients receiving evolocumab (1.5% vs. 1.9%, HR=0.79, 95% CI 0.66–0.95, p<0.01). Among the subgroup of patients with previous ischemic stroke (Giugliano et al. 2020**),** there were significantly fewer patients in the evolocumab group who experienced a primary end point event (259 vs. 300; HR= 0.85, 95% CI 0.72–1.00, p=0.047). A recent Cochrane review (Schmidt et al. 2017) included the results of 20 RCTs examining the use of additional PCSK9 inhibitors, such as alirocumab, in persons with and without established cardiovascular disease. Compared with placebo, at maximum follow-up of 6-36 months, treatment with a PCSK-9 inhibitor was associated with a significantly reduced risk of any cardiovascular events (OR=0.86, 95% CI 0.80 to 0.92) and any stroke (OR=0.77, 95% CI 0.69 to 0.85).

Icosapent ethyl is another example of an agent that can be added to a background statin regimen to reduce cardiovascular events. In the REDUCE-IT trial (Bhatt et al. 2019), 8,179 patients with established cardiovascular disease or with diabetes and other risk factors, who had a fasting triglyceride level of 1.52 to 5.63 mmol per liter and an LDL level of 1.06 to 2.59 mmol per liter were randomized to receive two grams of icosapent ethyl twice daily or placebo. After a median of 4.9 years, the risk of the primary outcome (a composite of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina), was significantly lower in the icosapent ethyl group (17.2% vs. 22%; HR=0.75, 95% CI 0.68-0.83, p<0.001, NNT=21). The risk of ischemic stroke was also significantly lower in the icosapent ethyl group (2.0% vs. 3.0%, HR=0.64, 95% CI 0.49, 0.85).

Sex and Gender Considerations:
There does not appear to be a sex difference associated with increasing cholesterol levels and risk of stroke. Data from 34 studies included in a meta-analysis found that for each 1-mmol/L increase in total cholesterol the risks of any stroke were increased by 1% in women, and 3% in men (Peters et al. 2016). The pooled ratio of relative risks was 0.99 (95% CI 0.93- 1.04). The corresponding risks for

ischemic stroke were increased by 16% in women, and 9% in men, with a pooled ratio of relative risks of 1.09 (95% CI 0.94-1.27). In the Cholesterol Treatment Trialists' Collaboration study examining sex differences (Fulcher et al. 2015), which included 27 RCTs, statin therapy reduced the risk of major vascular events similarly in men and women. For each 1 mmol/L decrease in LDL cholesterol, the risk of stroke was reduced by 17% in men and 10% for women (p>0.05).
Lipid Management Evidence Tables and Reference List

5.0 Diabetes Management in Stroke

Note: These recommendations are applicable to ischemic stroke, transient ischemic attack, and intracerebral hemorrhage.

Section 5 Recommendations 2020

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

5.1 Diabetes Screening and Assessment

i. Patients with ischemic stroke or transient ischemic attack should be screened for diabetes with either a fasting plasma glucose, or 2-hour plasma glucose, or glycated hemoglobin (A1C), or 75 g oral glucose tolerance test in either an inpatient or outpatient setting [Evidence Level C]. *Refer to Diabetes Canada guidelines for details on screening methods.*

ii. For patients with diabetes and either ischemic stroke or transient ischemic attack, glycated hemoglobin (A1C) should be considered as part of a comprehensive stroke assessment [Evidence Level B].

Refer to Prevention of Stroke Section 3 for information on blood pressure management in an individual with stroke and diabetes; refer to Prevention of Stroke Section 4 for information on lipid management in an individual with stroke and diabetes.

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 transient ischemic attack), as this target provides strong benefits for the prevention of microvascular complications [Evidence Level A]. *For frail elderly populations, please refer to the current Diabetes Canada guidelines for target A1C levels at www.diabetes.ca*

   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 to 7.0 mmol/L [Evidence Level B].

   c. The 2-hour postprandial plasma glucose target is 5.0 to 10.0 mmol/L [Evidence Level B].

   d. If A1C targets cannot be achieved with a postprandial target of 5.0 to 10.0 mmol/L, further postprandial blood glucose lowering, to 5.0 to 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 (for example, SGLT-2 inhibitors or GLP-1 receptor agonists) should be considered [Evidence Level B].

Note: For further recommendations on the use of SGLT-2 inhibitors and GLP-1 receptor agonists, please refer to the current Diabetes Canada guidelines at www.diabetes.ca.

Section 5.2 Clinical Consideration (New 2020):

i. The *Pioglitazone after Ischemic Stroke or Transient Ischemic Attack* trial (Kernan WN, Viscoli CM, Furie KL, et al, 2016) 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/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.

Refer to the current Diabetes Canada Clinical Practice Guidelines for additional information.

Rationale

Diabetes is a major risk factor for cardiovascular disease and is recognized as an independent risk factor for ischemic stroke. The risk of stroke is 50% higher in persons with diabetes. Most adults with type 1 or type 2 diabetes should be considered at high risk for vascular disease. The exceptions are younger adults with type 1 and type 2 diabetes with shorter duration of disease and without complications of diabetes (including established cardiovascular disease) and without other cardiovascular disease risk factors. Diabetes increases the risk of stroke and is a particularly potent risk factor in younger individuals, with studies suggesting an increase in stroke risk of as much as 10-fold in some younger subgroups. Overall, diabetes is considered a major risk factor for many conditions and is considered here as part of a comprehensive package supporting prevention and lifestyle management.

Diabetes education has been identified as a key priority for people following a stroke, who receive a new diagnosis of diabetes at the time of stroke. Those with prior history of diabetes have reported lack of understanding on the risks of stroke in people with diabetes, often citing they thought it was only a risk for heart disease, and not being aware of the connection with broader vascular risks. Several people with stroke who also experienced heart conditions stated their blood glucose levels were monitored and discussed only during those appointments and questioned why stroke care did not include the same management. Areas of concern voiced by people who have experienced stroke include whether they were tested for diabetes, the results of that testing, any cautions going forward or, if diabetes detected, they wanted to know how, when and by whom they were going to receive follow up care. Feedback from people who have experienced stroke and their families emphasized the silos that exist in the current healthcare system and the need to provide seamless and coordinated care following a stroke, especially considering the number of people living with multiple comorbid conditions.

System Implications

1. Coordinated diabetes awareness programs at the provincial and community levels that involve community groups, primary care providers (including physicians, nurse practitioners and pharmacists), and other relevant partners.
2. Coordinated education and support programs for persons with diabetes to increase adherence and reduce ongoing risks for cardiovascular complications.
3. Increased availability and access to education programs for healthcare providers across the continuum of care on management of patients with diabetes and stroke
4. Continued alignment with recommendations and guidelines developed by Diabetes Canada.
5. Universal and equitable access to cost-effective medicines for all people in Canada, regardless of geography, age, or ability to pay.

Performance Measures

1. Proportion of the population with a confirmed diagnosis of diabetes (type 1 and type 2).
2. Proportion of persons with diabetes presenting to hospital with a new stroke event.
3. Proportion of patients presenting to hospital with a stroke who receive a subsequent diagnosis of diabetes during their hospitalization for stroke care.

Measurement Notes

1. Performance measure 1: Rates may be obtained for Canada from the Public Health Agency of Canada Diabetes Surveillance database.
2. Performance measures 1 and 2 should be standardized for age and sex.
3. Data sources may include clinician order sheets, physicians' or nurses' notes, discharge summaries, or copies of prescriptions given to patients.
4. Blood values should be taken from official laboratory reports where possible.
5. Trends and benchmarks may be monitored and tracked through the National Diabetes Surveillance System data.
6.

Implementation Resources and Knowledge Transfer Tools

Health Care Provider Information

- Heart & Stroke: Post-Stroke Checklist: https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/002-17_csbp_post_stroke_checklist_85x11_en_v1
- Diabetes Canada Clinical Practice Guidelines: http://guidelines.diabetes.ca/
- Diabetes Canada professional resources: http://guidelines.diabetes.ca/healthcareprovidertools

Patient Information

- Heart & Stroke: Post-Stroke Checklist: https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/002-17_csbp_post_stroke_checklist_85x11_en_v1
- Heart & Stroke: Your Stroke Journey: https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/en-your-stroke-journey-v21
- Heart & Stroke: Online and Peer Support https://www.heartandstroke.ca/heart-disease/recovery-and-support/the-power-of-community
- Heart & Stroke: Resource: Diabetes: https://www.heartandstroke.ca/heart-disease/risk-and-prevention/condition-risk-factors/diabetes
- Diabetes Canada: http://www.diabetes.ca/
- Diabetes Canada patient resources: http://guidelines.diabetes.ca/PatientResources.aspx

Summary of the Evidence 2020

In persons with diabetes, the risk of stroke, particularly ischemic stroke is increased. Estimates from the InterStroke 1 study (O'Donnell et al. 2010) suggested that the odds of any stroke were increased by 36% among those with diabetes (60% for ischemic stroke). More recent estimates from the Interstroke 2 study (O'Donnell et al. 2016), are lower at 16% and 33% for any and ischemic stroke, respectively, although the population attributable risks (PAR) are similar between studies. The PAR for ischemic stroke was 7.9% in Interstroke 1 and was 7.5% in the Interstroke 2 study. The independent contribution of diabetes is difficult to determine, since many risk factors for stroke, including hypertension, dyslipidemia and atrial fibrillation, are found more frequently in those with diabetes. The higher stroke risk may be due to the complex interplay between the various hemodynamic and

metabolic components of the diabetes syndrome. In addition to the traditional risk factors, those specifically associated with the metabolic syndrome (insulin resistance, central obesity, impaired glucose tolerance and hyperinsulinemia), which are common in diabetes, also contribute to the increased risk. In persons with diabetes, stroke outcomes are worse, and are associated with increased mortality, more residual neurologic and functional disability and longer hospital stays. Lifestyle changes, tight glycemic control, antiplatelet drugs, such as aspirin and control of lipid levels with statins can all have beneficial effects. Blood pressure control is another vital aspect in reducing risk, and a number of recent studies have provided evidence supporting the use of angiotensin converting enzyme (ACE) inhibitors as first-line treatment in patients with diabetes.

Intensive blood glucose management to reduce stroke and cardiovascular risk has been studied in several large RCTs. The Action to Control Cardiovascular Risk in Diabetes Study (ACCORD, glucose-lowering arm) investigators (Gerstein et al. 2008) assessed whether intensive therapy to target normal glycated hemoglobin (HbA1c) levels would reduce cardiovascular events in patients with type 2 diabetes who had either established cardiovascular disease or additional cardiovascular risk factors. In this study, 10,251 patients with a median HbA1c level of 8.1% were randomly assigned to receive intensive therapy using multiple drugs including insulins and oral hypoglycemia agents, (targeting an HbA1c level <6.0%) or standard therapy (targeting a level from 7.0%-7.9%). The trial was stopped early due to mortality trends suggesting an increased rate of death from any cause associated with intensive therapy (HR=1.22, 95% CI 1.01-1.46, p=0.04). Although at 4 months, mean HbA1c values had fallen to 6.7% (intensive group) and 7.5% (control group), there was no reduction in the risk of the primary outcome (nonfatal MI, nonfatal stroke or death from cardiovascular causes) associated with intensive glucose lowering (6.9% vs. 7.2%, HR=0.90, 95% CI 0.78-1.04, p=0.16). Patients in the intensive group required medical assistance for hypoglycemia more frequently (10.5% vs. 3.5%), and greater proportions gained >10 kg from baseline (27.8% vs. 14.1%) and experienced a serious nonhypoglycemic adverse event (2.2% vs. 1.6%). Another trial that examined intensive glucose control in persons with poorly-controlled diabetes was the Veterans Affairs Diabetes Trial (Duckworth et al. 2009). After a median duration of follow-up of 5.6 years, HbA1c values were significantly lower in the intensive glucose control group; however, there were no significant differences between groups on any of the primary or secondary outcomes, including the risk of stroke (26 vs. 36 events, HR=0.78, 95% CI 0.48-1.28) or TIA (19 vs. 13, HR=1.48, 95% CI 0.73-2.99). There were significantly more hypoglycemic events in the intensive therapy group. The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial (Patel et al. 2008) randomly assigned patients (n = 11,140) with type 2 diabetes to undergo either standard glucose control or intensive glucose control, defined as the use of gliclazide (modified release) plus other drugs as required to achieve an HbA1c value of 6.5% or less. After a median of 5 years of follow- up, the mean HbA1c level was lower in the intensive-control group (6.5%) than in the standard-control group (7.3%). Intensive control reduced the incidence of combined major macrovascular and microvascular events (18.1% v. 20.0% with standard control; HR 0.90, 95% CI 0.82–0.98; p=0.01), as well as that of major microvascular events (9.4% v. 10.9%; HR 0.86, 95% CI 0.77–0.97; p=0.01), primarily because of a reduction in the incidence of nephropathy (4.1% v. 5.2%; HR 0.79, 95% CI 0.66–0.93; p=0.006), with no significant effect on retinopathy (p=0.50). There was no significant difference between groups in the risk of death from any cause (HR=0.93, 95% CI 0.83-1.06, p=0.28) or in the risk of fatal or nonfatal stroke or all cerebrovascular events associated with intensive intervention. Severe hypoglycemia was significantly more frequent in the intensive treatment group (HR=1.86, 95% CI 1.42-2.40, p<0.001). The results of these three trials and UK Prospective Diabetes Studies 33 and 34 were included in a meta-analysis (Marso et al. 2010) which examined the benefit of intensive glycemic control for the prevention of vascular events, among persons with type 2 diabetes. At the end of follow-up (mean of 5

years), the mean HbA1c values were 6.6% (intensive) and 7.4% (control). There was no reduction in the risk of all-cause mortality, stroke or cardiovascular mortality associated with intensive glycemic treatment; however, there was a significant 14% reduction in nonfatal myocardial infarction (RR=0.86, 95% CI 0.77-0.97, p=0.015).

Additional agents can also be added to standard regimens to improve glycemic control in patients with type 2 diabetes who have trouble achieving their blood glucose targets. One such agent is selective inhibitor of sodium glucose cotransporter (SGLT-2), which has been shown to reduce glycated hemoglobin levels and improve cardiovascular outcomes. Recent RCTs include CREDENCE (Perkovic et al. 2019, Mahaffey et al. 2019), DECLARE–TIMI 58 (Wiviott et al. 2019), CANVAS (Neal et al. 2017, Zhou et al. 2019) and EMPA-REG OUTCOME (Zinman et al. 2015). The proportion of patients with established atherosclerotic cardiovascular disease in these trials was 50% (CREDENCE), 40.6% (DECLARE), 65.6% (CANVAS) and 100% (EMPA-REG). A systematic review & meta-analysis including the results from three of these trials (EMPA-REG OUTCOME, CANVAS Program, and DECLARE-TIMI 58), which compared empagliflozin, canagliflozin and dapagliflozin vs. placebo, reported SGLT2 reduced the risk of a major adverse cardiac event by 11% (HR=0·89, 95% CI 0·83–0·96, p=0·0014); however, the benefit was only seen in persons with established atherosclerotic CVD. The overall risk of ischemic stroke was not reduced significantly in the SGLT2 group (HR=0.97, 95% CI 0.86-1.10), nor was the risk reduced significantly in persons with established atherosclerotic CVD, or in those with multiple risk factors (Zelniker et al. 2018). The CREDENCE trial was stopped prematurely due to efficacy. After a median of 2.6 years of follow-up, the event rate of the primary outcome (a composite of end stage kidney disease, doubling of the serum creatinine level, or renal or cardiovascular death) was significantly lower in the canagliflozin group (43.2 vs. 61.2 per 1000 patient-years; HR= 0.70; 95% CI 0.59 to 0.82). The risk was reduced significantly in both the primary and secondary prevention groups. The risk of cardiovascular death, myocardial infarction or stroke was also reduced significantly by 20%.

The glucagon-like peptide 1 receptor (GLP-1), liraglutide, is another example of an agent that may be added to standard regimes. Many large, RCTs have evaluated their effectiveness within the past 5 years, including REWIND (Gerstein et al. 2019), PIONEER 6, (Husain et al. 2019), HARMONY (Hernandez et al. 2018), EXCEL (Holman et al. 2017), SUSTAIN-6 (Marso et al. 2016) and LEADER (Marso et al. 2016). All of these trials included persons with type 2 diabetes, with established cardiovascular risk factors +/- a previous cardiovascular event who were treated with various GLP-1 agents (albiglutide, liraglutide, semaglutide, exenatide, dulaglutide) or placebo for a duration of 2.1 to 5.4 years. The risk of the primary outcome, major cardiovascular event, was reduced significantly from 8% to 24%. When the results of these trials were included in two systematic reviews, the risk of nonfatal and total stroke were significantly lower in the treatment group, with no significant reduction in the risk of fatal stroke (Barkas et al. 2019, Bellastella et al. 2019).

Insulin resistance, while widespread in persons with type 2 diabetes, is also present in persons who have suffered a stroke or TIA. Treatment with Pioglitazone has recently been investigated (Kernan et al. 2016). In the Insulin Resistance After Stroke (IRIS) study, 3,876 patients, ≥40 years with stroke or TIA within previous 6 months, with insulin resistance were randomized to receive pioglitazone with a target dose of 45 mg daily or placebo for 5 years. The risk of the primary outcome (fatal or non-fatal myocardial infarction or fatal or non-fatal stroke) was significantly lower for patients in the pioglitazone group (9.0% vs. 11.8%, HR=0.76, 95% CI 0.62-0.93, p=0.007), as was the risk of the development of diabetes over the study period (3.8% vs. 7.7%, HR=0.48, 95% CI 0.33-0.69, p<0.001). The risk of stroke was not significantly reduced for patients in the pioglitazone group (6.5% vs. 8.0%, HR=0.82,

95% CI 0.61-1.10, p=0.19) and the frequency of adverse events including bone fracture, weight gain, edema, shortness of breath and liver enzyme abnormalities was significantly higher in the pioglitazone group. In another trial (*PROspective pioglitAzone Clinical Trial In macroVascular Events*), treatment with pioglitazone for persons with type 2 diabetes and extensive macrovascular disease did not reduce the risk of the primary outcome (HR=0.90, 95% CI 0.80-1.02, p=0.095) or the risk of stroke (HR=0.81, 95% CI 0.61-1.07), after an average of 32 months (Dormandy et al. 2005).

Diabetes Management Evidence Tables and Reference List

6.0 Antiplatelet Therapy for Ischemic Stroke and Transient Ischemic Attack

Section 6 Recommendations 2020

6.1 Acute Antiplatelet Therapy

i. All patients with acute ischemic stroke or transient ischemic attack 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 hours of symptom onset (ideally within 12 hours) [Evidence Level B].

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

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

For ongoing antiplatelet therapy, refer to Section 6.2.

Refer to CSBPR Acute Stroke Management Module Section 7 for additional information.

6.2 Antiplatelet Therapy for Secondary Stroke Prevention

Note: These recommendations are applicable to ischemic stroke and transient ischemic attack.

i. For patients with ischemic stroke or transient ischemic attack, 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 hours of symptom onset (ideally within 12 hours) [Evidence Level B].

iii. For long-term secondary stroke prevention, either acetylsalicylic acid (80 mg – 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 transient ischemic attack 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 days 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 days following a transient ischemic attack 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 days [Evidence Level B]. Patients should be counseled that dual antiplatelet therapy with acetylsalicylic acid and clopidogrel should continue for only 21 days, 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 mg - 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 days [Evidence Level B].

viii. **(NEW FOR 2020):**: For patients with a recent stroke or transient ischemic attack 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

i. 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.

ii. **(NEW FOR 2020):** Pharmacogenetic testing can identify patients with clopidogrel resistance, however its clinical implications for stroke prevention treatment are unclear at this time.

iii. **(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.

Rationale

Antiplatelet agents are considered a fundamental component of secondary stroke prevention. Several clinical trials have shown that antiplatelet medications (such as acetylsalicylic acid) reduce the risk of further vascular events after transient ischemic attack or ischemic stroke (25 percent relative risk reduction). This effect is modest and is clinically useful because antiplatelet therapy is tolerated by the majority of patients who have had a transient ischemic attack or ischemic stroke. Trials comparing different antiplatelet therapy regimes show quite small absolute differences in efficacy, rendering the options equivocal.

Many people with stroke, and their families, often worry about being on ‘blood thinners’ and potential risks and side effects. They often feel like thy lack the information they need to manage antiplatelet agents appropriately and often rely on their pharmacist as their main source of education on

antiplatelet medications they were prescribed. They also stated that this was the fastest and easiest way to get information on their medications. People with stroke would like information about antiplatelet agents provided and reinforced, including why they are being prescribed these medications and the associated risk factors. Difficulties were expressed when seeing multiple specialists and receiving conflicting information from them, specifically about these medications. This highlights the need for proper transition planning and effective communication strategies between specialists and family doctors to improve adherence and safety in medication management, prevent errors and reduce adverse events.

System Implications

1. Stroke prevention clinics accessible in each community to improve secondary stroke prevention (including effective, consistent prevention with early recognition of risk factors and timely, targeted interventions).
2. Coordinated and comprehensive stroke prevention should be offered by primary care providers, and a mechanism in place to ensure that stroke risk is addressed during encounters with healthcare professionals throughout the continuum of care.
3. Improved communication and transition planning between all stages and settings of care and ensuring that primary care team members are fully informed on the goals of care, prevention therapies initiated by the healthcare providers during first assessments (e.g., in the emergency department), follow-up appointments for further investigations and longterm management.
4. Optimization of comprehensive stroke strategies at the local, regional, and provincial levels to prevent the recurrence of stroke.
5. Stroke prevention awareness and education about secondary prevention for primary care practitioners and specialists who manage stroke patients during the acute phase and after discharge from acute care.

Performance Measures

1. Proportion of acute ischemic stroke and transient ischemic attack patients who receive acute antiplatelet therapy within the first 48 hours of hospital arrival.
2. Proportion of patients with ischemic stroke or transient ischemic attack prescribed antiplatelet therapy on discharge from acute care.
3. Proportion of patients with ischemic stroke or transient ischemic attack prescribed antiplatelet therapy on discharge from secondary prevention clinic care.

Measurement Notes

1. Data sources include patient chart, nurses' notes, physicians' orders, and discharge summary note. Documentation quality may affect ability to accurately monitor this performance measure.
2. It may be a challenge to measure compliance and prescribing patterns in primary care.
3. Some patients may be on anticoagulants and would therefore be considered exclusions to these measures. See *Canadian Stroke Strategy Performance Measurement Manual* for additional measures on all antithrombotic prescribing (www.canadianstrokestrategy.ca).
4. Reasons potentially eligible patients are not prescribed antiplatelet agents should be included in data collection. This information may contribute to the interpretation of the findings of the performance measures and guide quality improvement initiatives.

Implementation Resources and Knowledge Transfer Tools

Health Care Provider Information

- Heart & Stroke: Post-Stroke Checklist:

https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/002-17_csbp_post_stroke_checklist_85x11_en_v1

- CSBPR: Acute Stroke Management, Acute Antiplatelet Therapy
  https://www.strokebestpractices.ca/recommendations/acute-stroke-management
- Canadian Cardiovascular Society Antiplatelet Therapy Guidelines:
  https://www.onlinecjc.ca/article/S0828-282X(17)31221-7/abstract
  https://ccs.ca/guidelines-and-position-statement-library/
- CHEST Antithrombotic Guidelines:
  https://journal.chestnet.org/GuidelineAntithrombotic
- Canadian Cardiovascular Society Guideline Resource:
  https://ccs.ca/guideline-resources/
- Canadian Cardiovascular Society Antiplatelet Therapy Knowledge Translation Program
  http://www.ccsguidelineprograms.ca/ccs-antiplatelet-therapy/
- Thrombosis Canada clinical guides: https://thrombosiscanada.ca/clinicalguides/
- CLOT PLUS "CLOT+ is a continuously updated repository of current best evidence from research to support evidence-based clinical decisions." https://plus.mcmaster.ca/ClotPlus/

Patient Information

- Heart & Stroke: Post-Stroke Checklist:
  https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/002-17_csbp_post_stroke_checklist_85x11_en_v1
- Heart & Stroke: Your Stroke Journey:
  https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/en-your-stroke-journey-v21
- Heart & Stroke: Online and Peer Support
  https://www.heartandstroke.ca/heart-disease/recovery-and-support/the-power-of-community
- Heart & Stroke Antiplatelets:
  https://www.heartandstroke.ca/heart-disease/treatments/medications/antiplatelet-medications
- Thrombosis Canada Patient and Family Information:
  https://thrombosiscanada.ca/resourcepage/patient-family-information/

Summary of the Evidence 2020

The use of antithrombotic agents in patients who have experienced an ischemic stroke or transient ischemic attack has been shown to reduce the risk of future events. The most commonly recommended antiplatelet agents for secondary stroke prevention in North America and Europe are acetylsalicylic acid (ASA, 75 to 325 mg/day), clopidogrel, and the combination of ASA and extended-release dipyridamole.

ASA Monotherapy

The benefit of long-term acetylsalicylic acid (ASA) or aspirin use for secondary prevention is well established. Daily, low-dose ASA reduces the risk of vascular events including myocardial infarction (MI), stroke, and vascular death in patients who have experienced a previous vascular event or who are at high risk of vascular disease. The Antithrombotic Trialists' Collaboration (ATTC, 2002) included the results of 287 RCTs (n=135,000) examining any antiplatelet therapy for the prevention of vascular events in high-risk patients. In 9 of these trials, long-term ASA monotherapy was associated with an

11% reduction in the odds a future vascular event (8.2% vs. 9.1%) among patients with a previous stroke or transient ischemic attack. In 65 trials examining ASA monotherapy, the mean percentage odds reduction of any vascular event, across doses ranging from <75 mg to 1,500 mg, was 23%. Treatment with ASA reduced the number of serious vascular events by 36 per 1,000 per year over two years in patients with a previous history of stroke or transient ischemic attack, compared with placebo. In the 2009 update of the ATTC systematic review, which included 16 secondary prevention trials, there was a significantly reduced risk of any subsequent stroke (RR=0.81, 95% CI 0.68-0.96) associated with ASA therapy, although the risk of major gastrointestinal and other extracranial bleeds was significantly increased.

Antiplatelet Therapy Following Stroke

Long-term treatment with both mono and dual antiplatelet therapy has been shown to reduce the risk of recurrent vascular events in persons with previous cardiovascular/cerebrovascular events. Using the results from 6 RCTs (CAPRIE, ESPS-2, MATCH, CHARISMA, ESPRIT, and PRoFESS), Greving et al. (2019) reported the combination of aspirin/dipyridamole significantly reduced the risk of serious vascular events compared with aspirin monotherapy (RR= 0.83; 95% CI, 0.74–0.94), as did clopidogrel monotherapy (RR= 0.88; 95% CI, 0.78–0.98), and aspirin/clopidogrel combination (RR=0.83; 95% CI, 0.71–0.96); however, only the combination of aspirin + dipyridamole significantly reduced the risk of recurrent ischemic stroke (RR=0.86, 95% CI 0.76–0.97). Combining safety and efficacy outcomes, the highest-ranking net clinical benefit outcome (serious vascular events or major bleeding) profile was achieved by clopidogrel and aspirin/dipyridamole combination (RR=0.89; 95% CI 0.82–0.96 and RR=0.87; 95% CI 0.80–0.95, respectively). Yang et al. (2018) also reported dual antiplatelet therapy (vs. monotherapy) significantly reduced the risk of recurrent stroke (RR=0.69, 95% CI 0.61-0.78) and major vascular events (RR= 0.72, 95%CI 0.64 to 0.80), but increased the risk of major bleeding, in a meta-analysis that included the results of 18 RCTs.

Dual vs. Monotherapy with Clopidogrel

The short-term use of the combination of clopidogrel + aspirin vs. aspirin alone, has been shown to reduce the risk of additional ischemic vascular events within 90 days. The Platelet-Oriented Inhibition in New TIA & Minor Ischemic Stroke (POINT) Trial enrolled 4,881 patients with recent (within previous 12 hours) minor stroke or transient ischemic attack (Johnston et al. 2018). Patients were randomized to receive 81 mg aspirin + 75 mg clopidogrel or aspirin + placebo, for 90 days. The risks of ischemic and hemorrhagic stroke were significantly lower in the clopidogrel group (4.6% vs. 6.3%; HR=0.72, 95% CI 0.56–0.92, and 4.8% vs. 6.4%; HR=0.74, 95% CI 0.58–0.94, respectively), although the risk of major hemorrhage was significantly increased (0.9% vs. 0.4%, HR=2.32, 95% CI 1.10–4.87, p= 0.02). The authors estimated that for every 1,000 patients treated with combination therapy for 90 days, 15 ischemic strokes would be prevented but 5 major hemorrhages would result. The Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial, randomized 5,170 patients with minor ischemic stroke, sustained within the previous 24 hours or high-risk transient ischemic attack, to receive clopidogrel (75 mg/day) plus low-dose ASA (75 mg/day) or clopidogrel placebo plus aspirin for 90 days (Wang et al. 2013). Significantly fewer patients in the clopidogrel + aspirin group experienced a stroke within 90 days (any stroke: 8.2% vs. 11.7%, HR=0.68, 95% CI 0.0.57-0.81 or an MI, stroke or vascular death stroke (8.4% vs. 11.9%, HR=0.69, 95% CI 0.58- 0.82). There was no difference in (any) bleeding events between groups (2.3% vs. 1.6%, p=0.09). The generalizability of the results of this trial have been questioned as the trial was conducted in China, which has a higher incidence of stroke compared with North America. Pan et al. (2019) conducted a patient-level meta-analysis, using the results from the POINT and CHANCE trials. The risks of a major ischemic event, ischemic stroke, disabling or fatal stroke and nondisabling stroke were all reduced

significantly with dual antiplatelet therapy, while the risk of hemorrhagic events was not increased significantly. The risk of a major ischemic event associated with dual antiplatelet therapy was reduced significantly from days 0-21(overall), and from days 0-10, but not from days 11-21, or days 22-90. A meta-analysis including the results from 13 RCTs, with a mean duration of follow-up of one-year (Palacio et al. 2015) reported the use of clopidogrel plus aspirin was associated with significantly reduced odds of any stroke compared with aspirin alone (OR=0.81, 95% CI 0.74-0.89). The odds were reduced for patients with stable vascular disease (OR=0.82, 95% CI 0.69-0.97) and for patients with a recent vascular event (OR=0.84, 95% CI 0.72-0.98); however, the use of dual therapy was associated with a significant increase in the odds of major hemorrhage (OR=1.40, 95% CI 1.26-1.55). Among the 4 RCTs that included patients with recent ischemic stroke (CARESS, CHARISMA, CLAIR, FASTER), the odds of all stroke were significantly reduced (OR=0.67, 95% CI 0.46-0.97) after a median of one-year follow-up, while the odds of major hemorrhage were not significantly increased (OR=0.91, 95% CI 0.40-2.07).

Ticagrelor

Although used more frequently to prevent coronary thrombotic events, ticagrelor is another antiplatelet agent that has been shown to reduce the risk of ischemic stroke when used as both a monotherapy (compared with aspirin) and in combination with aspirin. In the SOCRATES Trial, Johnston et al. (2016) included 13,199 patients ≥40 years, who had suffered a minor acute ischemic stroke (NIHSS score of ≤5) or high-risk transient ischemic attack ($ABCD^2$ score of ≥4) or with symptomatic intracranial or extracranial arterial stenosis, to be randomized to receive either ticagrelor (loading dose of 180 mg, followed by 180 mg daily for days 2-90 + aspirin placebo) or aspirin (loading dose of 300 mg, followed by 300 mg daily for days 2-90+ ticagrelor placebo) within 24 hours after symptom onset. Although the p-values were not considered significant on the basis of their statistical plan, by 90 days there were fewer occurrence of both ischemic stroke and all stroke in the ticagrelor group (5.8% vs. 6.7%, HR=0.87, 95% CI 0.76-1.00, and 5.9% vs. 6.8%, HR=0.86, 95% CI 0.75-0.99, respectively). By 90 days, the primary outcome (first occurrence of any event from the composite of stroke, MI, or death) occurred in 6.7% of patients in the ticagrelor group vs. 7.5% in the aspirin group (HR=0.89, 95% CI 0.78-1.01, p=0.007). When combined with 75 to 100 mg of aspirin daily, 90 mg of ticagrelor twice daily, the risk of recurrent stroke or death was significantly reduced in the dual therapy group compared with aspirin alone (5.5% vs. 6.6%, HR=0.83, 95% CI 0.71-0.96, p=0.02) in the THALES trial (Johnston et al. 2020). The risk of ischemic stroke was also significantly lower in the ticagrelor–aspirin group (5.0% vs. 6.3%, HR=0.79, 95% CI 0.63-0.94, p=0.04), although the risk of severe bleeding and intracranial hemorrhage or fatal bleeding were each four times higher in the ticagrelor–aspirin group.

Novel Oral Anticoagulants

While anticoagulants are known to reduce the risk of embolic stroke in patients with atrial fibrillation, Hart et al (2018) hypothesized that they might be more effective than antiplatelet therapy for the prevention of recurrent stroke in patients with recent embolic stroke of undetermined source. In the NAVIGATE ESUS trial, 7,213 patients with an ischemic, non-lacunar stroke of undetermined source were randomized to receive 15 mg rivaroxaban + aspirin placebo or 100 mg of enteric coated aspirin + rivaroxaban placebo. The trial was terminated early due to an excess risk of bleeding among patients in the rivaroxaban group and an absence of benefit. The primary efficacy outcome (ischemic or hemorrhagic stroke or systemic embolism) occurred in 172 patients in the rivaroxaban group (annualized rate, 5.1%) and in 160 in the aspirin group (annualized rate, 4.8%) (HR=1.07; 95% CI, 0.87 to 1.33; p=0.52). Similarly, the use of dabigatran did not reduce the risk of recurrent stroke in the RE-SPECT ESUS Trial (Diener et al. 2019). 5,390 patients ≥60 years, with stroke of undetermined source, sustained within the previous 3 months, or with at least one vascular risk factor identified within the

previous 6 months, were randomized to receive 150 or 110 mg depending on age and kidney function) dabigatran twice daily or 100 mg plain aspirin once daily. After a median duration of follow-up of 19 months, the risk of recurrent stroke was not reduced significantly in the dabigatran group (4.1% vs. 6.6%, HR=0.85; 95% CI 0.69 to 1.03), nor was the risk of ischemic stroke (4.0% vs. 4.7% per year, HR=0.84, 95% CI 0.68–1.03). Although the risk of major bleeding was not increased significantly with dabigatran, the risk of clinically relevant nonmajor bleeding resulting in hospitalization, was increased (1.6% vs. 0.9% per year, HR= 1.73, 95% CI 1.17–2.54).

Sex and Gender Considerations:
There is no evidence of a differential effect of antiplatelet agents used for secondary stroke in women compared with men. For example, in the Antithrombotic Trialists' Collaborative (Baigent et al. 2009), using secondary prevention trials, the risk of ischemic stroke was not significantly different among aspirin users (men: RR= 0·73, 95% CI 0·50–1·06 vs. women: RR= 0·91, 95% CI 0·52–1·57). A patient-level network meta-analysis (Greving et al. 2019), examining mono or dual antiplatelet therapy for long-term secondary prevention reported there was no evidence of heterogeneity of treatment effect for sex, or any other prespecified subgroups for the outcome of serious vascular events.

Antiplatelet Therapy Evidence Tables and Reference List

7. Anticoagulant Therapy for Atrial Fibrillation

Section 7 Recommendations 2020

Notes:

These recommendations are applicable to ischemic stroke and transient ischemic attack.

These recommendations focus on atrial fibrillation in the context of secondary prevention of stroke. For information on the primary prevention of stroke in individuals with non-valvular atrial fibrillation (AF), please refer to the current Canadian Cardiovascular Society/Canadian Heart Rhythm Society (CCS/CHRS) Guidelines for the Management of Atrial Fibrillation: Prevention of Stroke and Systemic Thromboembolism in Atrial Fibrillation and Flutter (October 2020).

Definitions:

Non-valvular atrial fibrillation refers to atrial fibrillation in the absence of moderate to severe mitral stenosis or mechanical heart valve (CCS 2020 AF guideline).

DOAC refers to Direct (non-vitamin K) Oral Anticoagulant.

7.1 Detection of Atrial Fibrillation following Stroke.

i. Patients with suspected ischemic stroke or transient ischemic attack should have a 12-lead ECG to assess for atrial fibrillation, 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 transient ischemic attack, ECG monitoring for 24 hours 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 transient ischemic attack 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]. *Refer to CSBPR Secondary Prevention of Stroke Module for additional guidance in management of patients with stroke and atrial fibrillation, and the Canadian Cardiovascular Society current recommendations on atrial fibrillation.*

iv. **(NEW FOR 2020):** For patients aged >65 years with ischemic stroke or transient ischemic attack, 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 transient ischemic attack *and* atrial fibrillation should receive oral anticoagulant therapy for secondary stroke prevention [Evidence Level A]. *Refer to Appendix Four for additional information on selection of anticoagulant medications.*

   a. **(NEW FOR 2020):** For patients with an ischemic stroke or transient ischemic attack 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 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]. *Refer to Appendix Four for Selection of Anticoagulant Agents for Management of Atrial Fibrillation after stroke or transient ischemic attack.*

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]. *Refer to S*econdary *Prevention of Stroke Section on Antiplatelet Therapy for Ischemic Stroke and Transient Ischemic Attack for additional information.*

iii. For patients with ischemic stroke or transient ischemic attack 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 transient ischemic attack in patients with non-valvular atrial fibrillation who cannot receive long-term oral anticoagulant therapy, a left atrial appendage occlusion procedure may be considered [Evidence Level B]. *Refer to current Canadian Cardiovascular Society guideline for Atrial Fibrillation for additional information.*

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. Refer to Thrombosis Canada Clinical Guide for additional information regarding INR targets and concomitant acetylsalicylic acid for different valve types and locations (https://thrombosiscanada.ca/clinicalguides/#)*

vi. NEW RECOMMENDATION FOR 2020: For patients with atrial fibrillation who experience ischemic stroke or transient ischemic attack in spite of anticoagulant therapy, we recommend the following: (1) identify and address medication nonadherence; (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]. *Refer to current Canadian Cardiovascular Society guideline for Atrial Fibrillation secondary prevention of stroke section for additional information.*

Section 7.2 Clinical Considerations Revised for 2020:

Timing of Initiation of Oral Anticoagulant Therapy following Acute Stroke:

i. 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.

ii. 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 poststroke is as follows:

   a. For patients with a brief transient ischemic attack and no visible infarct or hemorrhage on imaging, anticoagulation may be started within the first 24 hours post- transient ischemic attack.

   b. For patients with a minor clinical stroke/small non-hemorrhagic infarct on imaging, anticoagulation may be started 3 days 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 days 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 days post-stroke.

iii. If anticoagulation is delayed beyond 24 hours, 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.

iv. 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, e.g., for some patients with large infarcts and those with hemorrhagic transformation.

Stroke while on DOAC Therapy

v. (NEW FOR 2020): For patients with atrial fibrillation who experience ischemic stroke or transient ischemic attack 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.

vi. 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 international normalized ratio 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 under-dosing 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]. *Refer to*

Appendix Four for Selection of Anticoagulant Agents for Management of Atrial Fibrillation after stroke or transient ischemic attack.

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]. *Refer to Section 7.2 (iv) for information on mechanical valves.*

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]. *Refer to current Canadian Cardiovascular Society Atrial Fibrillation guidelines for patients with recent coronary ischemic* events.

Refer to current Canadian Cardiovascular Society Atrial Fibrillation guidelines and Thrombosis Canada Clinical Guide for additional information on detection and management of atrial fibrillation.

Refer to Thrombosis Canada clinical guide for peri-operative management of patients on oral anticoagulant therapy at https://thrombosiscanada.ca/clinicalguides.

Rationale

Atrial fibrillation (AF) is a significant risk factor for stroke, and a strong example of the heart brain connection. One in six patients admitted to hospital in Canada with ischemic stroke have atrial fibrillation, and this proportion increases with age. Since AF can be paroxysmal and subclinical, AF may go undetected.

In the general population, people with atrial fibrillation who are not treated with anticoagulant therapy are at a 3 – to – 5 times increased risk of stroke. Most strokes in individuals with atrial fibrillation are potentially preventable with anticoagulant therapy. The number needed to treat (NNT) to prevent one recurrent stroke (i.e., secondary prevention) was 12 with warfarin (compared with placebo) (Hart 2007). The newer class of direct oral anticoagulants (DOAC) have been shown to be as effective as warfarin with decreased bleeding risk. The number needed to treat (NNT) to prevent one recurrent stroke (i.e., secondary prevention) when being treated with DOACs compared to warfarin has been reported at 65 (Park et al, 2019) and to prevent the composite outcome of recurrent stroke or major bleeding the NNT is 48. Detection of atrial fibrillation is a critical step in stroke workups. Searching for atrial fibrillation post-stroke with prolonged ECG monitoring has been found to increase detection rates significantly, thereby enabling treatment aimed at preventing recurrent stroke.

As with all management strategies aimed at reduction in recurrent stroke and transient ischemic attack, compliance by individuals who have had a stroke or transient ischemic attack is an important component of risk reduction and they often require support from their healthcare team and family to be successful. When discussing anticoagulation for atrial fibrillation, people who have experienced stroke emphasized the need for health professionals to understand the magnitude of the heart-brain connection and to explain this link clearly to patients and families. This is especially important for health professionals right from initial contact with someone experiencing a stroke, such as emergency department teams. Following stroke, individuals often experience challenges in managing new medications or maintaining previous prescriptions, and report confusion when

different members of their circle of care provide inconsistent guidance with regards to their anticoagulant medication.

System Implications

1. Increased public awareness of atrial fibrillation as a risk factor for stroke.
2. Establishment of stroke prevention clinics to improve secondary stroke prevention including management of atrial fibrillation in patients with stroke and transient ischemic attack (effective, consistent prevention with early recognition of risk factors and timely, targeted interventions).
3. A process for appropriate outpatient monitoring of patients' international normalized ratio and follow-up communication with patients taking anticoagulants.
4. Optimization of comprehensive strategies at the local, regional, and provincial levels to prevent the recurrence of stroke.
5. Stroke prevention awareness and education about secondary prevention for primary care practitioners and specialists who manage stroke patients during the acute phase and after discharge from acute care, including content regarding the heart-brain connection and the importance of integrated care that addresses vascular risk factors in a coordinated manner.
6. For patients taking warfarin, access to a dedicated anticoagulant management clinic is associated with better patient outcomes compared to routine medical care.
7. Universal and equitable access to cost-effective medicines for all people in Canada, regardless of ability to pay or geography, through private and/or public drug coverage plans which can help manage atrial fibrillation.

Performance Measures

1. Proportion of acute ischemic stroke patients with atrial fibrillation who are treated with anti-coagulant therapy.
2. Proportion of eligible stroke and transient ischemic attack patients with atrial fibrillation prescribed anticoagulant therapy on discharge from acute care.
3. Proportion of eligible stroke and transient ischemic attack patients with atrial fibrillation prescribed anticoagulant therapy after a visit to a secondary prevention clinic.
4. Proportion of atrial fibrillation patients taking anticoagulant therapy at the time of hospital admission for acute ischemic stroke or transient ischemic attack.
5. Proportion of atrial fibrillation patients with stroke or transient ischemic attack on antiplatelet therapy and not prescribed anticoagulant therapy.
6. Proportion of atrial fibrillation patients with stroke or transient ischemic attack continuing anticoagulant therapy at 3 months, 6 months, and 1 year following initiation of therapy.
7. For atrial fibrillation patients on warfarin, the proportion with an international normalized ratio in the therapeutic range at three months.

Implementation Resources and Knowledge Transfer Tools

Health Care Provider Information

- Heart & Stroke: Post-Stroke Checklist: https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/002-17_csbp_post_stroke_checklist_85x11_en_v1
- CSBPR: Secondary Prevention of Stroke: Appendix Four: Oral Anticoagulants for the Prevention of Stroke in Individuals with Atrial Fibrillation
- Canadian Cardiovascular Society: 2020 CCS/CHRS Comprehensive Guidelines for the Management of Atrial Fibrillation https://ccs.ca/guidelines-and-position-statement-library/

- Canadian Cardiovascular Society Atrial Fibrillation Pocket Guides: https://ccs.ca/pocket-guides/
- Canadian Cardiovascular Society tools (app, slide decks, pocket guides, e-learning): https://ccs.ca/guideline-resources/
- Thrombosis Canada Clinical guides: https://thrombosiscanada.ca/clinicalguides/
- Thrombosis Canada Clinical Tools (including Direct Oral Anticoagulant (DOAC) Follow-Up Checklist): https://thrombosiscanada.ca/tools/

Patient Information

- Heart & Stroke: Post-Stroke Checklist: https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/002-17_csbp_post_stroke_checklist_85x11_en_v1
- Heart & Stroke: Your Stroke Journey: https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/en-your-stroke-journey-v21
- Heart & Stroke: Online and Peer Support https://www.heartandstroke.ca/heart-disease/recovery-and-support/the-power-of-community
- Heart & Stroke: Atrial Fibrillation information: http://www.heartandstroke.ca/heart/conditions/atrial-fibrillation
- Heart & Stroke: Stroke medications resource: https://www.heartandstroke.ca/stroke/treatments/medications
- Heart & Stroke: Working with your doctor: www.heartandstroke.ca/heart-disease/recovery-and-support/working-with-your-doctor
- Thrombosis Canada Patient and Family Information: https://thrombosiscanada.ca/resourcepage/patient-family-information/

Summary of the Evidence 2020

Detecting Atrial Fibrillation

Atrial fibrillation (AF) is a common arrhythmia, associated with an increased risk of ischemic stroke. Detecting AF in patients following minor stroke or transient ischemic attack, is important particularly in those with a cryptogenic stroke or embolic stroke of unknown source, since once identified, it can be effectively managed. Typically, this entails a change from an antiplatelet to an anticoagulant. However, AF is under-diagnosed because it is frequently paroxysmal and asymptomatic, and patients do not routinely undergo prolonged screening. AF can be detected using a variety of methods including a12-lead electrocardiogram (ECG), Holter monitoring, event recorders and implantable devices.

Prolonged ECG monitoring using wearable or insertable devices has been shown to be effective for improving the detection of paroxysmal AF (numbers needed to screen range from 8-14), with longer monitoring durations associated with an increased probability of AF detection. A systematic review and meta-analysis (Tsivgoulis et al. 2019) included the results from 2 RCTs (FIND-AF and Crystal AF and 2 observational studies). The outcomes of persons who received prolonged cardiac monitoring (PCM) using implantable cardiac monitoring or ambulatory ECG monitoring, were compared with patients who received conventional (non-PCM) cardiac monitoring. Among persons who received PCM, AF was detected more frequently (RR=2.46; 95% CI, 1.61–3.76), the risk of recurrent stroke and recurrent stroke or transient ischemic attack during follow-up was significantly lower (RR=0.45; 95% CI, 0.21–0.97 and RR=0.49; 95% CI, 0.30–0.81, respectively) and anticoagulation therapy was initiated more frequently (RR=2.07; 95% CI, 1.36–3.17).

In the FIND-AF Randomized trial, Wachter et al. (2016) recruited 398 patients, >60 years admitted with acute ischemic stroke, within 7 days of symptom onset, in sinus rhythm at admission and without a history of AF. Patients were randomized to receive prolonged Holter ECG monitoring for 10 days, starting in the first week post stroke, and repeated at 3 and 6 months or standard care (an average of 73 hours of inpatient telemetry

plus an average of 24 hours of Holter monitoring). At both 6 and 12 months, detection of AF was significantly higher in the prolonged monitoring group (13.5% vs. 4.5% and 13.5% vs. 6.1%, respectively). The associated numbers needed to screen were 11 and 13. There were no significant differences between groups in stroke recurrence (2.5 vs. 4.5%, p=0.28) or death (3.0 vs. 4.5%, p=0.45). A UK trial (Higgins et al. 2013) that randomized 100 patients with no history of AF and in sinus rhythm, reported that a strategy of 7-day ECG monitoring in the acute phase post-stroke was superior to standard care for the detection of paroxysmal AF (18% vs. 2%; p<0.05). Significantly more patients who received additional monitoring were started on anticoagulants. Among persons with nonacute stroke, Gladstone et al. (2014), found 30-day ambulatory cardiac event monitor to be superior to repeat 24-hour Holter monitoring in identifying AF in 572 patients aged 52 to 96 years without known AF, who had sustained a cryptogenic ischemic stroke or transient ischemic attack within the previous 6 months. Atrial fibrillation lasting ≥30 seconds was detected more frequently in persons using the cardiac event monitor (16.1% vs. 3.2%, absolute difference, 12.9%; 95% CI 8.0 to 17.6; p<0.001; number needed to screen= 8). The cardiac event monitor was also more likely to identify cases of AF lasting longer than ≥2.5 minutes (9.9% vs. 2.5%, absolute difference, 7.4%, 95% CI, 3.4 to 11.3; p<0.001). By 90 days, oral anticoagulant therapy had been prescribed for more patients in the intervention group (18.6% vs. 11.1%, p=0.01). Three-quarters of AF cases identified in the intervention group were detected within the first 2 weeks of monitoring.

Warfarin

Warfarin is well established as an effective medication for reducing the risk of stroke in patients with AF and atrial flutter and has been evaluated in a variety of adjusted-dose regimens, alone and in combination with ASA, as well as in low intensity and fixed, mini-dose treatment plans. A systematic review & meta-analysis (Hart et al. 2007) included the results of 29 trials involving 28,044 patients who had non-valvular atrial fibrillation. Six of the included trials compared placebo with adjusted-dose warfarin (2,900 participants, 20% with previous stroke or transient ischemic attack). Treatment with adjusted dose warfarin was associated with a 64% reduction in all strokes (ARR= 2.7%/year, NNT=37 for primary prevention; ARR=8.4%/year, NNT=12 for secondary prevention of stroke) and a 67% reduction for ischemic stroke. Mean INRs ranged from 2.0 – 2.6 in primary prevention studies and was 2.9 in the only secondary prevention study included. In trials that compared the effectiveness of warfarin with other antiplatelets, including clopidogrel and dipyridamole, the use of warfarin was associated with a 37% reduction in all strokes (95% CI 23%- 48%). An increased risk of intracranial hemorrhage was found to be associated with the use of adjusted-dose warfarin, although it was very small (absolute risk=0.2%/year).

The Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study recruited 973 patients (12.5% with previous stroke or transient ischemic attack aged 75 years or greater from primary care and randomly assigned them to receive adjusted-dose warfarin (INR 2.0 - 3.0) or ASA (75 mg once daily) and followed them for a mean of 2.7 years (Mant et al. 2007). The primary endpoint was fatal or disabling stroke (ischemic or hemorrhagic), other intracranial hemorrhage, or clinically significant systemic embolism. There were fewer primary events among participants assigned to warfarin (21 strokes, 2 other intracranial hemorrhages, and 1 systemic embolus), compared to those assigned to ASA (48 primary events: 44 strokes, 1 other intracranial hemorrhage, and 3 systemic emboli). The corresponding annual risks were 1.8% vs. 3.8%, RRR=52%, 95% CI 20-72%, p=0.003. To prevent one event each year, the number needed to treat was 50. The annual risk of extracranial hemorrhage was 1.4% for patients assigned warfarin and 1.6% for those assigned ASA. A Cochrane review authored by Saxena & Koudstaal (2004) also examined the effectiveness of oral anticoagulants with antiplatelet therapy in individuals with non-rheumatic (non-valvular) AF and history of previous stroke or transient ischemic attack. Two RCTs were included. The European Atrial Fibrillation Trial (EAFT) included 455 patients within three months of transient ischemic attack or minor stroke who were randomly assigned to warfarin (INR 2.5 to 4.0) or ASA (300 mg/day) and followed for a mean of 2.3 years (EAFT 1993). The Studio Italiano Fibrillazione Atriale (SIFA) trial included 916 patients within 15 days of transient ischemic attack or minor stroke who were randomized to open-label warfarin (INR 2.0 to 3.5) or indobufen (a reversible platelet cyclooxygenase inhibitor, 100 or 200 mg twice a day), and followed for one year (Morocutti 1997). Pooled analysis of the 2 trials revealed a significant protective effect in favour of anti-coagulant therapy over antiplatelet therapy for all vascular events (OR=0.67, 95%CI 0.50, 0.91) and for recurrent stroke (OR=0.49, 95% CI 0.33, 0.72). In terms of absolute risk, anticoagulant therapy was associated with a risk of approximately 4% per year in both studies, whereas the risk was 10%/year and 5%/year for individuals assigned to treatment with antiplatelet therapy in the EAFT and SIFA study, respectively. Warfarin use was not associated with significant increases in the risk of intracranial bleeding. Although major extracranial bleeding complications occurred more often in patients on warfarin (OR=5.16, 95% CI 2.08–12.83), the absolute difference was small (2.8% vs. 0.9%/year in EAFT and 0.9% vs. 0%/year in SIFA).

Novel Anticoagulants (versus warfarin)

In response to some of the management challenges associated with warfarin use such as the need for frequent monitoring and food and drug interactions, several new (novel) oral anticoagulants have been developed. Dabigatran, one such agent, is a direct thrombin inhibitor with a serum half-life of 12 to 17 hours, which was evaluated in the landmark Randomized Evaluation of Long-term anticoagulant therapy (RE-LY) trial (Connolly et al. 2009), which included 18,113 patients with AF and at least one other stroke risk factor. Patients were randomly allocated to receive dabigatran (110 mg or 150 mg twice daily) or warfarin (adjusted to an INR of 2.0-3.0) and followed for a median of two years. The primary outcome was a composite of stroke or systemic embolism. Both doses of dabigatran were found to be non-inferior to warfarin therapy in terms of risk for stroke or systemic embolism. In addition, the fixed dose of 150 mg was superior to warfarin therapy for the primary study outcome (RR=0.66, 95% CI 0.53, 0.82, p<0.001). However, when the subgroup of patients with previous transient ischemic attack /stroke were analysed separately, neither the 110 mg dose of dabigatran nor the 150 mg dose was associated with significant reductions in risk for recurrent events when compared with warfarin (p=0.65 and p=0.34, respectively). Compared to warfarin, the risks for major bleeding events, including life-threatening bleeding, intracranial bleeding, and gastrointestinal bleeding, were reduced in the 110 mg group only (RR=0.80, 95% CI 0.69, 0.93, p = 0.003), while the 150 mg dose was associated with increased risk for gastrointestinal bleeding (RR=1.50, 95% CI 1.19, 1.89, p<0.001). During the long-term extension of the RELY-ABLE trial (Connolly et al. 2013), which included 5,851 participants who had been assigned to either of the dabigatran dosing schedules in the original trial, the annual rates of stroke or systemic embolism were 1.46% and 1.6% in the 150 mg and 110 mg dose groups, respectively. The risk of this combined outcome was not significantly different between groups (HR=0.91, 95% CI 0.69-1.20). Similarly, annual rates of ischemic stroke were 1.15% in the 150 mg group and 1.24% in the 110 mg group (HR=0.92, 95% CI 0.67, 1.27), with low incidences of hemorrhagic stroke and myocardial infarction in both groups. There was a significantly increased risk of bleeding events associated with the higher dose of dabigatran (3.74% vs. 2.99%; HR=1.26, 95% CI 1.04-1.53), although gastrointestinal bleeding events were similar in both groups (1.54% and 1.56%/year). Mortality was similar in both dose conditions (3.1% and 3.02% per year).

Three Factor Xa inhibitors, rivaroxaban, apixaban and edoxaban, have been investigated in large clinical trials. The results indicate they reduce the risk of recurrent vascular events, and lead to fewer hemorrhagic complications, compared with warfarin. In the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF, Patel et al. 2011), 14,264 patients with elevated risk for stroke were randomized to receive fixed-dose rivaroxaban (20 mg daily or 15 mg daily in patients with reduced creatinine clearance) or adjusted-dose warfarin (target INR of 2.0 to 3.0). The median length of treatment was 590 days. Stroke or systemic embolism occurred less frequently in patients who received rivaroxaban (1.7% vs. 2.2% per year; HR= 0.79; 95% CI 0.66-0.96, p<0.001 for non-inferiority). There were fewer incidences of intracranial hemorrhage in the rivaroxaban group (HR=0.67, 95% CI 0.47, 0.93; p=0.02), although the risk of major bleeding from a gastrointestinal site was increased (3.2% vs. 2.2%, p<0.001).

The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial (Granger et al. 2011) randomized 18,201 patients with AF and at least one other risk factor for stroke to treatment with apixaban (5 mg twice daily) or dose-adjusted warfarin (target INR 2.0-3.0). The primary outcome of stroke or systemic embolism occurred in significantly fewer patients in the apixaban group (212 vs 265; HR= 0.79; 95% CI 0.66- 0.95; p<0.001 for non-inferiority and p=0.01 for superiority). There was no between group difference for ischemic stroke alone (p=0.42); however, treatment with apixaban was associated with a significant reduction in risk for hemorrhagic stroke when compared to warfarin (HR=0.51, 95% CI 0.35-0.75; p<0.001). There was a significant reduction in risks of death from any cause and fatal or disabling stroke associated with apixaban (HR=0.89, 95% CI 0.80- 0.99; p=0.047 and HR=0.71; 95% CI, 0.54-0.94, respectively). Intracranial bleeding occurred more often in individuals assigned to treatment with warfarin (HR=0.42, 95% CI 0.3-0.58; p<0.001). The risk of major bleeding was significantly lower in the apixaban group (HR= 0.69; 95% CI, 0.60- 0.80; p<0.001). Overall, apixaban was found to be superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality.

The Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial (Giugliano et al. 2013) assessed the use of edoxaban versus warfarin in patients with atrial fibrillation. The trial randomized 21,105 patients to receive dose-adjusted warfarin, high-dose edoxaban (60mg), or low-dose edoxaban (30mg). The target INR for the warfarin group was 2.0-3.0 and the median duration of the treatment was 2.5 years. The primary efficacy outcome was the occurrence of stroke or systemic embolic event and the primary safety outcome was the occurrence of major bleeding during treatment. Patients in the high-dose and low-dose edoxaban groups experienced non-inferior rates of stroke and systemic embolic events compared to the patients receiving warfarin (HR 0.79, 97.5% CI 0.63 to 0.99, p<0.001 and HR 1.07, 97.5% CI 0.87 to 1.31, p=0.005). A superiority analysis for the annualized rate of stroke or systemic embolic event found no evidence for the superiority of either high-dose edoxaban (HR 0.87, 97.5%

CI 0.73 to 1.04, p=0.08) or low-dose edoxaban (HR 1.13, 97.5% CI 0.96 to 1.34, p=0.10) compared to warfarin. The safety profile of edoxaban was supported by significantly lower annualized rates of bleeding events for both high-dose and low-dose treatment regimens compared to warfarin (HR 0.8, 95% CI 0.71 to 0.91, p<0.001 and HR 0.47, 95% CI, 0.41 to 0.55, p<0.001).

Novel Anticoagulants (versus ASA)

In addition to comparison with warfarin, the potential benefit of NOACs has also been compared with ASA. In the NAVIGATE ESUS trial (Hart et al. 2018), 7,213 patients with an ischemic, non-lacunar stroke of undetermined source were randomized to receive 15 mg rivaroxaban + aspirin placebo or 100 mg of enteric coated aspirin + rivaroxaban placebo. The trial was terminated early due to an excess risk of bleeding among patients in the rivaroxaban group and an absence of benefit. The primary efficacy outcome (ischemic or hemorrhagic stroke or systemic embolism) occurred in 172 patients in the rivaroxaban group (annualized rate, 5.1%) and in 160 in the aspirin group (annualized rate, 4.8%) (HR=1.07; 95% CI, 0.87 to 1.33; p=0.52). A similar finding was reported in the RE-SPECT ESUS Trial (Diener et al. 2019). 5,390 patients ≥60 years, with stroke of undetermined source, sustained within the previous 3 months, or with at least one vascular risk factor identified within the previous 6 months, were randomized to receive 150 (or 110 mg depending on age and kidney function) dabigatran twice daily or 100 mg plain aspirin once daily. After a median duration of follow-up of 19 months, neither the risk of recurrent stroke, nor the risk of ischemic stroke was reduced significantly in the dabigatran group (4.1% vs. 6.6% and 4.0% vs. 4.7%, respectively). While the risk of major bleeding was not significantly higher in the dabigatran group (1.7% vs. 1.4% per year, HR= 1.19; 95% CI, 0.85 to 1.66), the risk of clinically relevant nonmajor bleeding was (1.6% vs. 0.9% per year, HR= 1.73, 95% CI 1.17–2.54), as was the risk of major or clinically relevant nonmajor bleeding (3.3% vs. 2.3% per year, HR=1.44, 95% CI 1.12–1.85).

Apixaban has also been compared with ASA in patients with AF. In the Apixaban Versus Acetylsalicylic Acid to Prevent Strokes in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES, Connolly et al. 2011) trial, 5,599 patients were randomized to receive apixaban 5 mg twice daily or ASA at a dose of 81 to 324 mg daily. The median length of follow-up was 1.1 years. The primary efficacy outcome was the occurrence of stroke (ischemic or hemorrhagic) or systemic embolism. The trial was terminated early given the clear benefit demonstrated in favour of apixaban. There were significantly fewer primary outcome events recorded in the apixaban condition than in the ASA condition (113 vs. 51, HR=0.45, 95% CI 0.32-0.62; p<0.001). For stroke events in particular, there were significantly fewer ischemic events in individuals treated with apixaban (HR=0.37, 95% CI 0.25-0.55; p<0.001), although there were no significant between group differences in hemorrhagic stroke (p=0.45). There was no difference in the incidence of major bleeding events between groups.

Mechanical Heart Valves

Lifelong anticoagulation is usually required for patients with prosthetic heart valve replacement due to the risk of thromboembolic complications; however, questions remain regarding the most appropriate regimens. Current Canadian guidelines recommend target INRs of 2.5-3.0, depending on the location of the replacement valve with a vitamin K antagonist (VKA). Puskas et al. (2014) evaluated whether a less aggressive target for anticoagulation could be as effective. In this study, 425 patients with elevated risk of thromboembolism, including chronic atrial fibrillation or left ventricular ejection fraction<30% were recruited in the Prospective Randomized On-X Valve Anticoagulation Clinical Trial (PROACT). In addition to receiving 81 mg aspirin daily, patients were randomized to a lower-dose warfarin group with a target INR of 1.5-2.0, or to a standard therapy group with a target INR=2.0-3.0 through self-management three months following aortic valve replacement. After a mean duration of just under 4 years, there were significantly fewer major, minor and total bleeding events in the lower-dose warfarin group (10 vs. 25, RR=0.45, 95% CI 0.21-0.94, p=0.032: p 8 vs. 25, RR=0.36, 95% CI 0.16-0.79, p=0.011 and 18 vs. 50, RR=0.40, 95% CI 0.24-0.69, p<0.001, respectively). The risks of hemorrhagic, ischemic stroke and transient ischemic attack were similar between groups (1 vs. 2, RR=0.56, 95% CI 0.001-10.7, p=0.63: 5 vs. 5, RR=1.12, 95% CI 0.32-3.87, p=0.859 and 9 vs. 6, RR=1.68, 95% CI 0.60-4.72. p=0.326, respectively). The potential benefit of dabigatran was examined in the Randomized, Phase II Study to Evaluate the Safety and Pharmokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement (RE-ALIGN). This trial randomized patients to warfarin with a target INR of 2-3, or 2.5-3.5 depending on thromboembolic risk, following aortic and/or mitral valve replacement, or two escalating doses of dabigatran for 12 weeks (Eikelboom et al. 2013). The trial was stopped early due to an excess of thromboembolic and bleeding events in the dabigatran group. Among patients in whom treatment was initiated within 7 days of valve replacement, there were 9 strokes and two TIAs in the dabigatran group and no strokes and two TIAs in the warfarin group, respectively. The addition of antiplatelets to VKA therapy following heart valve replacement was the topic of a Cochrane review (Massel & Little 2013), which included the results from

13 trials. The addition of either aspirin or dipyridamole significantly reduced the risk of thromboembolic events (OR= 0.43, 95% CI 0.32- 0.59, p < 0.00001) and total mortality (OR= 0.57, 95% CI 0.42- 0.78, p = 0.0004); however, the risk of major bleeding was increased significantly (OR=1.58, 95% CI 1.14- 2.18, p= 0.006).

Timing of Resumption of Anticoagulation Following Ischemic Stroke

It is generally agreed that anticoagulation can be resumed within the first two weeks following an ischemic stroke, although the exact timing remains uncertain. The results from several recent studies differ slightly. Yaghi et al. (2020) compared the outcomes of patients who initiated anticoagulation from 0-3 days (n=617), 4-14 days (n=535), or >14 days (n=137) following stroke. Overall, there was no significant difference in the primary composite endpoint (recurrent ischemic stroke, transient ischemic attack, and systemic arterial embolism, and sICH, or major extracranial hemorrhage) within 90 days, between the three groups: 0-3 days (10.3%), 4-14 days (9.7%) and >14 days (10.2%), p=0.933, nor was there a difference in the occurrence of anticoagulation related sICH between the 3 groups: 0-3 days (1.1%), 4-14 days (1.7%), and >14 days (2.9%), p=0.295). Wilson et al. (2019) compared the outcomes of patients with atrial fibrillation who reinitiated oral anticoagulation within 4 days of ischemic stroke or transient ischemic attack (n=358), ≥5 days or in those who did not resume OACs (n=997). After adjusting for all potential confounders, there was no increased risk of the of the composite outcome (transient ischemic attack, stroke, or death within 90 days) in the late OAC group compared with the early group (OR= 1.17, 95% CI 0.48 to 2.84), nor was there an increased risk of ischemic stroke or transient ischemic attack (OR=1.25, 95% CI 0.36 to 4.41). Multivariable sensitivity analyses comparing later (5 to 14 days) and very late OAC (≥15 days or not started at all) to early OAC (0 to 4 days) showed little difference in the odds of the primary composite outcome (OR= 1.19, 95% CI 0.45 to 3.90 and OR= 1.14, 95% CI 0.42 to 3.09, respectively). The RAF-NOAC trial (Paciaroni et al. 2017) included 1,127 patients, with acute ischemic stroke and known or newly diagnosed atrial fibrillation. All patients were initiated on NOACs. The timing of recurrent events including stroke, transient ischemic attack, systemic embolism, and symptomatic and major bleeding was examined in relation to the timing of NOACs. The risk of the primary outcome was not associated with the timing of initiation of NOACs (<3 days; OR=1.00 (ref), days 3-7: OR=1.30, 95% CI 0.54–3.71; days 8-14: OR=1.44, 95% CI, 0.36–3.02; >14 days: OR=0.59, 95% CI 0.15–1.95). 80% of patients received NOACs within the first 15 days following stroke. Results from the Early Recurrence and cerebral bleeding in patients with acute ischemic stroke and Atrial Fibrillation (RAF) study (Paciaroni et al. 2015) also suggest that the optimal window for initiation or resumption of treatment with anticoagulants is between 4-14 days following stroke. Of 1,029 patients admitted with acute ischemic stroke and known or newly diagnosed AF, significantly fewer patients treated with oral anticoagulants had a primary outcome event (composite of stroke, transient ischemic attack, symptomatic systemic embolism, symptomatic cerebral bleeding, and major extracerebral bleeding at 90 days) compared with patients treated with either LMWHs alone or LMWH followed by oral anticoagulants (7% vs. 16.8% and 12.3%, respectively, p=0.003). Adjusted for age, sex, CHA_2DS_2-VASc score, lesion size, reperfusion therapy, and NIHSS on admission, patients who had been initiated on treatment with anticoagulants between 4 and 14 days had a significantly reduced risk of the primary outcome and in ischemic events compared with patients who had their treatments initiated before 4 or after 14 days from stroke onset (HR=0.53, 95% CI 0.30–0.93, *p*=0.025 and HR=0.43, 95% CI 0.19–0.97, p=0.043, respectively).

Left Atrial Appendage (LAA) Devices

In patients with non-valvular AF, embolic stroke can occur through the formation of a thrombus in the left atrium. Several devices are available to exclude blood flow from the LAA, reducing stroke risk. The WATCHMAN device has been evaluated (for non-inferiority) in several large RCTs. In the Watchman Left Atrial Appendage System for Embolic Protection in Patients with AF (PROTECT-AF, Holmes et a. 2009), 707 patients with a $CHADS_2$ score of ≥1 were randomized to undergo LAA occlusion with the WATCHMAN device (n=463) or to continuing warfarin therapy (n=244). After a mean duration of follow-up of 18 months, the event rate/100 patient- years for the primary outcome (a composite of the occurrence of stroke, cardiovascular or unexplained death, or systemic embolism), was 3.0 for the intervention group vs. 4.9 for the control group (RR=0.62, 95%, Cr I 0.35 to1.25), which met the threshold for non-inferiority. However, the risk of events related to excessive bleeding was significantly higher in the intervention group (7.4 vs. 4.4/100 patient-years). The Watchman LAA Closure Device in Patients with Atrial Fibrillation Versus Long Term Warfarin Therapy (PREVAIL) study (Holmes et al. 2014) was similar to PROTECT-AF, in terms of treatment contrasts and eligibility criteria. In this trial, which included 407 participants, the mean age was slightly older and the proportion of patients with a $CHADS_2$ score of ≥2 was higher. While the results of this trial failed to demonstrate non-inferiority of the WATCHMAN device compared with warfarin for the reduction of the early primary efficacy endpoint (a composite of ischemic or hemorrhagic stroke, systemic embolism and cardiovascular death), evidence of non-inferiority was reached for the late primary efficacy endpoint (events excluding the first 7 days post procedure). A patient-level meta-

analysis (Holmes et al. 2015) including the results from the PREVAIL and PROTECT-AF trials reported the risk of the primary outcome (stroke, systemic embolization and CV death) was not significantly different between groups (2.72 per 100-person years for device and 3.50 for warfarin; HR=0.79, 95% CI 0.53 to 1.2, p=0.22). The risk of hemorrhagic stroke was significantly lower in the device group (HR=0.22; 95% CI 0.08 to 0.61), as was the risk of CV/unexplained death (HR= 0.48,95% CI: 0.28 to 0.8).

Sex and Gender Considerations

Although the prevalence of atrial fibrillation (AF) is known to be higher in men, women may suffer the consequences disproportionately more. A systematic review (Emdin et al. 2016) including 30 studies with 4,371,714 participants found that was associated with a higher risk of all-cause mortality in women (ratio of relative risks for women compared with men 1.12, 95% CI 1.07 to 1.17) and a significantly higher risk of stroke and cardiovascular mortality. While women were less likely to receive oral anticoagulants (OAC) after a recent diagnosis of AF in the PINNACLE study (Thompson et al. 2017), (56.7% vs. 61.3%; P<0.001), there was no evidence of a difference in OAC use in the GARFIELD-AF study (60.9% of men versus 60.8% of women) (Lip et al. 2015). In terms of treatment efficacy, women with AF taking warfarin were at a significantly greater residual risk of stroke and other systemic embolism compared with men, while there were no differences between sexes for treatment with novel oral anticoagulants (Pancholy et al. 2014).

Ko et al (2017) reported that many RCTs were not powered to study sex-specific differences in primary or secondary outcomes, which might contribute to false-negative findings. Their ability to derive sex-specific results is further limited by underrepresentation of women in cardiovascular disease prevention trials. Only 25–30% of the participants in the major trials of warfarin were women. The proportion of women participants has increased in trials of the non-vitamin K antagonist oral anticoagulants (NOACs) to approximately 40%, to reflect more accurately the relative prevalence of AF in women compared with men.

Anticoagulant Therapy for Atrial Fibrillation Evidence Tables and Reference List

8. Perioperative Management of Anticoagulant and Antiplatelet Therapy

This is a new section added for 7th Edition, 2020.

Definitions

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

Refer to current Thrombosis Canada Guidance and Perioperative Anticoagulant Management Algorithm for additional information.

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 [Level of Evidence B].

ii. For patients with atrial fibrillation receiving a Direct Oral Anticoagulant (**DOAC)** for stroke prevention who require temporary DOAC interruption for an elective surgery or procedure, the following approach is recommended [Level of Evidence 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 days total), and restart the day after the procedure.

   b. For a **high-bleed-risk** surgery or procedure, stop the DOAC 2 days before the procedure, the day of the procedure, and one day after the procedure (i.e., skip 4 days total).

   Note: An exception involves patients on dabigatran with impaired renal function (CrCl <50 mL/min) in whom an additional 1-2 days 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 days pre-procedure, and resumed within 24 hours post-procedure, without heparin bridging [Level of Evidence: 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 days before and 3 days

after the surgery or procedure [Level of Evidence: 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 [Level of Evidence: B]. *Refer to current Thrombosis Canada Guidance and Perioperative Anticoagulant Management Algorithm for additional information.*

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 days pre-procedure is recommended and should be resumed within 24 hours post-procedure [Level of Evidence: 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) [Level of Evidence: 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 [Level of Evidence: B].

v. For patients receiving **acetylsalicylic acid** for stroke prevention who require an elective or urgent (within 7 days) carotid endarterectomy or coronary artery bypass surgery, acetylsalicylic acid should be continued without interruption [Level of Evidence: 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 carotid endarterectomy (within 7 days), acetylsalicylic acid and a P2Y12 inhibitor should be continued perioperatively [Level of Evidence 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 days [Level of Evidence C].

Section 8 Clinical Considerations

Perioperative management of patients undergoing a minimal-bleed-risk procedure

i. 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 hours 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 international normalized ratio (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 where the likelihood of polypectomy or multiple biopsies is low.

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

i. Patients having a **high-bleed-risk** surgery or procedure only need to be off DOACs for 2 days before the procedure, corresponding to a 60–68-hour 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-hour half-life of DOACs.

ii. Patients having a **low/moderate-bleed-risk** surgery or procedure only need to be off DOACs for 1 day before the procedure, corresponding to a 36–42-hour interval between the last dose and the surgery.

iii. For all patients, no DOAC should be taken on the day of surgery/procedure.

iv. 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 days before a high-bleed-risk surgery: 2 days before a low/moderate-bleed-risk surgery).

v. Postoperative resumption of DOACs should wait at least 24 hours after a low/moderate-bleed-risk surgery or procedure and 48-72 hours after a high-bleed-risk surgery or procedure.

vi. There are caveats to postoperative DOAC management: First, the 48–72-hour resumption interval can be extended if there is greater than expected postoperative 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 LMWH can be given for the initial 1-3 postoperative days

Rationale

The perioperative management of patients receiving anticoagulant therapy is a common issue. The aim is to minimize the risk of stroke and other thromboembolic events while simultaneously minimizing the risk of clinically important (major) bleeding.

System Implications

1. Processes in place for access to pre-operative consultation prior to invasive surgery or procedures to optimize patient safety.

Performance Measures

1. Percentage of people with a history of stroke on antithrombotic agents who experience a perioperative/peri-procedural stroke.
2. Median length of stay people for with a history of stroke on antithrombotic agents who experience a perioperative/peri-procedural stroke compared to same population without peri-operative stroke.

Implementation Resources and Knowledge Transfer Tools

Health Care Provider Information

- Heart & Stroke: Post-Stroke Checklist: https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/002-17_csbp_post_stroke_checklist_85x11_en_v1
- Thrombosis Canada Clinical guides https://thrombosiscanada.ca/clinicalguides/
- Thrombosis Canada Clinical Tools:

https://thrombosiscanada.ca/tools/

- Antithrombotic Therapy and Prevention of Thrombosis: CHEST Evidence-Based Clinical Practice Guidelines: https://journal.chestnet.org/GuidelineAntithrombotic

Patient Information

- Heart & Stroke: Post-Stroke Checklist: https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/002-17_csbp_post_stroke_checklist_85x11_en_v1
- Heart & Stroke: Your Stroke Journey: https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/en-your-stroke-journey-v21
- Heart & Stroke: Online and Peer Support https://www.heartandstroke.ca/heart-disease/recovery-and-support/the-power-of-community
- Heart & Stroke: Stroke medications resource: https://www.heartandstroke.ca/stroke/treatments/medications
- Thrombosis Canada Patient and Family Information: https://thrombosiscanada.ca/resourcepage/patient-family-information/

Summary of the Evidence 2020

Heparin bridging and warfarin interruption.

Heparin bridging is used in selected warfarin-treated patients and, typically, consists of giving a low-molecular-weight heparin (LMWH), such as enoxaparin 1 mg/kg BID or dalteparin 100 IU/kg BID, for 3 days before a surgery, during warfarin interruption. The premise of heparin bridging is that it shortens the time around the surgery that patients are not fully anticoagulated, while warfarin is interrupted and resumed, with the aim of mitigating the risk for stroke and systemic embolism.

In patients with atrial fibrillation who are receiving warfarin, there is evidence from the BRIDGE trial that heparin bridging had no effect on preventing arterial thromboembolism but increased the risk for major bleeding. Rates of arterial thromboembolism were 0.3% and 0.4% in patients who were bridged and not bridged, but rates of major bleeding were significantly higher in patients who were bridged: 3.2% vs. 1.3%. One caveat to the study findings is that heparin bridging might be considered in selected high-risk patients, including those with a $CHADS_2$ score of 5-6 or those who have had perioperative thromboembolism during prior interruption of warfarin. In patients with a mechanical heart valve who require warfarin interruption, heparin bridging is suggested, especially in patients with a mitral valve prosthesis or any older tilting disc or caged-ball prosthesis. However, in selected patients, especially those having a high-bleed-risk surgery or procedure, we suggest omitting post-operative heparin bridging. Preoperative INR testing is not routinely needed but can be done in patients having a high-bleed-risk surgery or neuraxial anesthesia. An INR >1.5 on the day before the surgery can be managed by giving 1-2 mg oral vitamin K. After surgery, INR testing can be done in patients who are receiving heparin bridging can be stopped once the INR is >2.0.

Perioperative management of DOAC therapy

In DOAC-treated patients who require treatment interruption for an elective surgery or procedure, patient management is based on the estimated bleed risk associated with the surgery or procedure. Thromboembolic risk is less of a concern because the duration of anticoagulant interruption is short as DOACs have a rapid offset and onset of action. Perioperative heparin bridging and coagulation function testing are not routinely needed for perioperative DOAC management. There are selected patients in whom low-dose LWWH can be used after surgery, typically if they are at increased risk for venous thromboembolism and cannot take their DOAC medication by mouth.

Postoperative management of DOAC therapy

Postoperative resumption of DOACs should mirror preoperative interruption, so as to wait at least 24 hours after a low/moderate-bleed-risk surgery or procedure and 48-72 hours after a high-bleed-risk surgery or procedure. This approach was assessed in a prospective study, PAUSE, which studied 3,007 DOAC-treated patients (1,257 on apixaban, 668 on dabigatran and 1,082 on rivaroxaban) who required an elective surgery or procedure. The strategy of standardized DOAC interruption and resumption, no perioperative bridging and no preoperative coagulation function testing appeared safe as the 30-day postoperative rates of arterial thromboembolism, and major bleeding were <1% and <2%, respectively.

In summary, a quick way to remember perioperative DOAC management for an elective surgery or procedure is: "*1 day off before and after a low/moderate-bleed-risk procedure and 2 days off before and after a high-bleed-risk procedure*".

Perioperative management of antiplatelet therapy

The perioperative management of patients receiving antiplatelet therapy such as acetylsalicylic acid, clopidogrel or both, and require an elective surgery/procedure is common because of the widespread use of these drugs for the secondary prevention of stroke and myocardial ischemia. The aim of perioperative antiplatelet management is to minimize the risk of stroke and myocardial ischemia while simultaneously mitigating the risk of bleeding which, if it occurs, can lead to prolonged antiplatelet interruption that, in turn, may increase the risk for stroke or cardiovascular events.

Most antiplatelet drugs (acetylsalicylic acid, clopidogrel, prasugrel) irreversibly inhibit platelet function for the lifespan of the platelet, which is 7-10 days. Consequently, platelet function is restored by 10-15% for each day such agents are interrupted. Ticagrelor reversibly inhibits platelets and, consequently, normalization of platelet function occurs within 2-3 days after interruption. Dipyridamole, a pyridopyridamine derivative with antiplatelet and anticoagulant properties and a half-life of 8 hours, has reversible antiplatelet effects but when it is combined with acetylsalicylic acid for secondary stroke prevention, this reversibility is nullified. There are few high-quality randomized trials to inform perioperative antiplatelet management and these studies have focused on patients who are receiving acetylsalicylic acid alone. Studies assessing patients who are receiving acetylsalicylic acid and a $P2Y_{12}$ inhibitor and require an elective surgery are mainly retrospective studies.

Taken together, these studies suggest that in patients taking acetylsalicylic acid who need non-cardiac surgery, acetylsalicylic acid should be continued perioperatively in selected patients at increased risk for cardiovascular events, such as those with a prior stroke or coronary stent. Caution is warranted when continuing ASA without interruption in patients undergoing a high-bleed-risk surgery/procedure.

For patients taking acetylsalicylic acid who need coronary artery bypass or carotid artery surgery, acetylsalicylic acid is continued perioperatively. If a patient is also taking a $P2Y_{12}$ inhibitor, this is typically interrupted for 5 days before coronary artery bypass surgery and 7 days before other non-cardiac surgery. For patients taking acetylsalicylic acid and a $P2Y_{12}$ inhibitor who need urgent carotid artery surgery, typically within 1-2 weeks of a stroke syndrome, there is limited evidence from retrospective studies suggesting benefit with continuing both antiplatelet agents but with an associated increase in perioperative bleeding. In such patient's pre-operative discussion with the surgeon of the benefits and risks of this management is advisable.

Sex and Gender Considerations

No studies were found that address sex and gender differences on this topic.

Perioperative management of anticoagulant and antiplatelet therapy Evidence Tables and Reference List

Table 8. Suggested Management of Antiplatelet Therapy for Elective Surgery

Legend: *ASA, acetylsalicylic acid; CABG, coronary artery bypass graft.*

Clinical Situation	Suggested Pre- and Post-operative Management
Patient receiving ASA alone having non-cardiac surgery	• interrupt ASA 7-10 days before surgery in most patients; resume 5-7 days after surgery • consider continuing ASA, **without interruption,** in patients with a prior stroke **or a coronary stent** • **continue ASA, without interruption, in patients having carotid endarterectomy**
Patient receiving ASA alone and having CABG surgery	• continue ASA around the time of CABG, **without interruption***
Patient receiving ASA + clopidogrel and having non-cardiac surgery**	• continue ASA around the time of surgery, **without interruption*** • hold clopidogrel 5-7 days pre-operatively and resume 1-2 days after surgery
Patient receiving ASA + clopidogrel and having CABG surgery	• continue ASA around the time of surgery, **without interruption*** • hold clopidogrel at least 5 days before surgery • resume clopidogrel 1-2 days after surgery
Patient receiving ASA + ticagrelor and having non-cardiac or CABG surgery	• continue ASA around the time of surgery, **without interruption*** • hold ticagrelor at least 2 days before surgery • resume ticagrelor 1-2 days after surgery
Patient receiving ASA + prasugrel and having non-cardiac or CABG surgery	• continue ASA around the time of surgery, **without interruption*** • hold prasugrel 7-10 days before surgery • resume prasugrel 1-2 days after surgery

** Continue ASA, without interruption* - This implies that ASA is taken on the day of surgery and the first postoperative day, acknowledging that there may be circumstances when this is not feasible (e.g., patient cannot take medications by mouth); in such cases, management is left to the treating clinician with the option to administer ASA per rectum.*

*** Patient receiving ASA + clopidogrel and having non-cardiac surgery** - Management should be individualized depending on the clinical indication for dual antiplatelet therapy and, typically, would require consultation with other specialists, for example, a cardiologist in patients with a coronary stent.*

In patients who are taking Aggrenox (ASA + dipyridamole) for a prior stroke and are having carotid endarterectomy, Aggrenox can be continued without interruption; alternatively, Aggrenox can be withheld on the day of surgery to eliminate the added antiplatelet effect of dipyridamole while retaining the antiplatelet effect of ASA."

9. Management of Extracranial Carotid Artery Disease and Intracranial Atherosclerosis

Note: These recommendations are applicable to ischemic stroke and transient ischemic attack.

Definitions

Carotid stenosis is termed symptomatic if associated with a Symptomatic Event: ipsilateral carotid-territory cerebral or retinal ischemic event (ischemic stroke, transient ischemic attack, transient monocular blindness, or retinal artery occlusion) within the preceding 6 months.

Carotid endarterectomy (CEA): surgical removal of atherosclerotic plaques within an extracranial carotid artery, usually the common carotid and proximal internal carotid artery, to prevent thromboembolic stroke.

Carotid Artery Stenting (CAS): a minimally invasive endovascular procedure in which a stent (a slender, metal-mesh tube) is inserted into the area of narrowing to prevent thromboembolic stroke events by keeping the artery open and compressing plaque against the artery walls, this also includes potentially both pre- and post-balloon catheter dilatation (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].

Please refer to section on Acute Stroke Management, section 4.2 Neurovascular (Brain and Vascular) Imaging for details regarding vascular and brain parenchymal imaging for patients with suspected stroke or transient ischemic attack.

9.1.2 Indications for carotid revascularization

i. Patients with a symptomatic event attributed to an ipsilateral **50 to 99** percent 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 to 99** percent and women with **70 to 99** percent symptomatic carotid artery stenosis, carotid endarterectomy (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 periprocedural stroke and death rates of 5% [Evidence Level B].

ii. Carotid endarterectomy 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].

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 days [Evidence Level A].

ii. In **men with 50-69** percent stenosis the benefit of CEA is greatest when performed within 14 days of the qualifying event [Evidence Level A] and is attenuated when performed beyond 14 days of the qualifying event (*Refer to Table 9 below for summary of recurrent stroke risk at various time points).*

Section 9.1 Clinical Considerations

i. 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.

ii. 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.

iii. It may be reasonable to consider delaying CEA beyond 48 hours 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 transient ischemic attack.

iv. 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.

v. In acute stroke patients with tandem lesions (cervical carotid stenosis or occlusion and ipsilateral intracranial large vessel occlusion) who have undergone 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 (for example, blood pressure, diabetes, cholesterol, antiplatelet therapy, smoking cessation, and lifestyle changes) [Evidence Level B].

ii. Carotid endarterectomy may be considered for **highly selected patients with 60 to 99 percent** 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 carotid endarterectomy for **women with 60-99 percent** 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 carotid endarterectomy, 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, carotid endarterectomy should be performed by a surgeon who routinely audits their performance results and demonstrates a less than 3 percent 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 to 99 percent asymptomatic** carotid stenosis who are not operative candidates for technical, anatomic or medical reasons provided there is a less than 3 percent risk of peri-procedural morbidity and mortality [Evidence Level A].

Section 9.2 Clinical Considerations:

i. 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 (ex. 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 transient ischemic attack due to symptomatic **intracranial artery stenosis of 70-99 percent**, medical therapy is recommended over stenting for secondary stroke prevention [Evidence Level B].

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 transient ischemic attack 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 transient ischemic attack 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 uncertainty about the comparative efficacy of antiplatelet therapy vs. 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

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

Refer to Section One for recommendations on urgent vascular imaging in patients with acute transient ischemic attack and non-disabling stroke.

Refer to Section 2 on aggressive prevention management, and Section 6 on antiplatelet therapy.

Rationale

Carotid endarterectomy is a surgical procedure that removes atherosclerotic plaque from the proximal internal carotid artery. Successful carotid endarterectomy substantially reduces the risk of recurrent stroke in patients who present with a hemispheric transient ischemic attack or minor stroke and an ipsilateral high-grade carotid stenosis. One death or severe stroke is prevented for every six patients with symptomatic severe (70 to 99 percent) carotid stenosis treated with carotid endarterectomy, and

one for every 22 patients treated with stenosis less than 70 percent (Rothwell 2004; Orrapin, et al, 2017). For selected patients with asymptomatic carotid stenosis, carotid endarterectomy reduces the risk of stroke from about two percent per year to about one percent per year. Aggressive medical management was superior to intracranial stenting for patients with 70 to 99% stenosis of a major intracranial artery.

People who have experienced stroke and their families have reported that they received minimal education on carotid stenosis, and they wanted to learn more as this is an area not often included in general information on stroke.

System Implications

1. Protocols to ensure timely access to diagnostic services for evaluating carotid arteries.
2. Development of agreements and processes for rapid access to surgical consults, including a mechanism for expedited referrals as required for carotid interventions.
3. Ensure navigation of system is supported increasing patient compliance. Mechanisms to increase compliance should be explored and assessed.

Performance Measures

1. Proportion of stroke or transient ischemic attack patients with moderate to severe (50 percent to 99 percent) symptomatic carotid artery stenosis who undergo a carotid revascularization procedure following an index stroke/transient ischemic attack event. (KQI)
2. Proportion of stroke/transient ischemic attack patients with moderate to severe (50 percent to 99 percent) carotid artery stenosis who undergo a carotid revascularization procedure following an index event within 2 weeks of first hospital or SPC assessment. (KQI)
3. Median time from onset of index ischemic stroke or transient ischemic attack symptoms to carotid revascularization (days, hours). (KQI)
4. Proportion of stroke patients requiring carotid intervention who undergo the procedure within two weeks of the index stroke event.
5. Proportion of stroke patients with moderate carotid stenosis (50 percent to 69 percent) who undergo carotid intervention procedure following the index stroke event.
6. Proportion of stroke patients with mild carotid stenosis (less than 50 percent) who undergo carotid intervention procedure following the index stroke event.
7. Proportion of carotid endarterectomy patients who experience perioperative in-hospital stroke, acute myocardial infarction, or death.
8. The 30-day in-hospital mortality rate after carotid endarterectomy and stroke rate by carotid occlusion severity.
9. Proportion of patients who undergo carotid endarterectomy within two weeks, between two and four weeks, between four weeks and three months, and between three and six months of stroke onset.
10. Proportion of patients who wait more than three months for carotid endarterectomy or whose surgery is cancelled because of long wait times. Proportion of patients who experience a subsequent stroke event or death while waiting for carotid endarterectomy.

Measurement Notes

1. Time interval measurements should be taken from the time the patient or family reports as the time of stroke symptom onset to the actual date of surgery.
2. The stroke onset time will depend on patient report or that of a reliable observer at the time of the event.

3. Analysis should be stratified between those patients undergoing carotid stenting and those patients undergoing carotid endarterectomy, by severity of stenosis and by whether the patient had symptomatic or asymptomatic carotid artery disease.
4. Data source for surgical date should be surgical notes, nurses' notes, and discharge summary.
5. In some cases, it may be more appropriate or relevant to record the time interval from the first time the patient has contact with medical care until the time of carotid surgery. This has occurred in cases where the patient was out of the country at the time of the stroke event and chose to return to Canada before seeking definitive medical intervention. It is important to note the nature of the start time when calculating turnaround times or intervention times.

Implementation Resources and Knowledge Transfer Tools

Health Care Provider Information

- CSBPR: Acute Stroke Management, Neurovascular Imaging
  https://www.strokebestpractices.ca/recommendations/acute-stroke-management
- Question and Answers about carotid endarterectomy NINDS:
  http://www.ninds.nih.gov/disorders/stroke/carotid_endarterectomy_backgrounder.htm
- University of Oxford – Medical Sciences Division, Carotid Stenosis Tool. 1 year and 5-year risk of ipsilateral ischemic stroke predicted by model
  https://www.ndcn.ox.ac.uk/divisions/cpsd/carotid-stenosis-tool

Patient Information

- Heart & Stroke: Post-Stroke Checklist:
  https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/002-17_csbp_post_stroke_checklist_85x11_en_v1
- Heart & Stroke: Your Stroke Journey:
  https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/en-your-stroke-journey-v21
- Heart & Stroke: Online and Peer Support
  https://www.heartandstroke.ca/heart-disease/recovery-and-support/the-power-of-community
- Heart & Stroke: Atherosclerosis:
  https://www.heartandstroke.ca/heart-disease/conditions/atherosclerosis
- National Heart, Lung and Blood Institute:
  http://www.nhlbi.nih.gov/health/health-topics/topics/carend/

Summary of the Evidence 2020

Carotid Endarterectomy

Carotid endarterectomy (CEA) has been shown to be beneficial for preventing stroke recurrence in patients who have sustained a minor stroke or TIA with ipsilateral high-grade carotid stenosis. There are three large trials comparing endarterectomy for symptomatic stenosis with best medical treatment in such patients: The North American Symptomatic Carotid Endarterectomy Trial (NASCET, 1991), the European Carotid Surgery Trial (ECST, 1998) and the Veterans Affairs Trial (Mayberg et al. 1991). The results of these three trials were pooled in a Cochrane review (Rerkasem & Rothwell 2011). The risk of any stroke or operative death at 5-years in patients with severe stenosis (70–99%) was significantly reduced in patients in the CEA group (RR=0.53, 0.42-0.67, p<0.0001, NNT=6) with an associated absolute risk reduction of 16.0%. For patients with moderate stenosis (50-69%) the risk was also reduced (RR=0.77, 0.63- 0.94, p=0.001, NNT=22). For patients with mild stenosis, there was no benefit

of treatment. Perioperative death or stroke incidence was 7.0% (95% CI 6.2 to 8.0). The greatest benefit of treatment was found in men, patients aged 75 years or over, and patients randomised within two weeks after their last ischaemic event.

The use of CEA for asymptomatic carotid artery disease is more controversial, given that it is a lower-risk condition. Significant improvements have been made in the medical management of stroke risk factors during the previous 20 years, including the use of statins, antihypertensive agents, and antiplatelets or anticoagulants. Using data from the Asymptomatic Carotid Emboli Study (ACES), which included 477 patients with at least 70% carotid stenosis and no symptoms in the carotid artery territory for at least the previous 2 years, the use of antiplatelet and antihypertensive agents were both significant independent predictors of lower stroke risk or TIA at the end of the follow-up period (King et al. 2013). There are three large trials that have evaluated the risks and benefits of CEA in the asymptomatic group. The Asymptomatic Carotid Atherosclerosis Study (ACAS) Group, the MRC [Medical Research Council] Asymptomatic Carotid Surgery Trial (ACST) Collaborative Trial and the Veterans Affairs Trial. The results of these trials were pooled in a Cochrane review (Chambers & Donnan 2008). Median duration of follow-up ranged from 2.7-4.0 years. Although the risk of perioperative stroke death was higher in the CEA group (3.0% vs. 0.46%, RR= 6.49, 95% CI 2.53-16.61, p<0.0001), CEA was associated with significant reductions in the risk of perioperative stroke or death or subsequent ipsilateral stroke, (RR=0.71, 95% CI 0.55-0.90, p= 0.0051) as well as stroke or death or any subsequent stroke (RR= 0.69, 95% CI 0.57- 0.83, p<0.0001). The greatest benefits were evident in men and younger patients. There were insufficient data to determine whether increasing degree of stenosis was associated with increasing benefit from surgery. In 10-year follow-up of ACST (Halliday et al. 2010) in which patients were randomized to receive immediate treatment vs. delayed, immediate CEA was associated with a reduced occurrence of stroke at both 5 and 10 years (6.4% vs. 11.8%, p<0.0001 and 10.8% vs. 16.9%, p<0.0001, respectively). The authors concluded that despite a 3% perioperative stroke or death rate, CEA for asymptomatic carotid stenosis reduced the risk of ipsilateral stroke, and any stroke, by approximately 30% over three years, while acknowledging that the absolute risk reduction with carotid endarterectomy is small (1%/year).

Carotid Artery Stenting vs. Best Medical Management

Carotid-artery angioplasty with stenting emerged (CAS) has emerged as an alternative to carotid endarterectomy in patients at high risk for complications for endarterectomy such as contralateral occlusion, advanced age or severe coronary artery disease. The percutaneous approach also avoids the risks of general anesthesia and the local complications of neck hematoma, infection, cervical strain and cranial nerve damage associated with endarterectomy and requires a shorter recovery period. Several large trials assessing the safety and effectiveness of CAS (without the use of embolic protection devices) have been conducted.

The Stenting and Aggressive Medical Management for Preventing Stroke in Intracranial Stenosis (SAMMPRIS) trial, was the first large open-label clinical trial that randomly assigned patients who had a recent transient ischemic attack or stroke attributed to severe stenosis to receive aggressive medical management alone or aggressive medical management plus percutaneous transluminal angioplasty with stenting (PTAS), using the Wingspan stent system (Chimowitz et al. 2011). The primary end point was stroke or death within 30 days after enrollment or after a revascularization procedure for the qualifying lesion during the follow-up period or stroke in the territory of the qualifying artery beyond 30 days. Enrollment was stopped after 451 patients were enrolled because there was a significant increase in the number of patients in the PTAS group had a primary outcome event (20.5% vs. 11.5%, p=0.009). There was also an increased number of patients in the PTAS group who experienced any stroke during the study period (22.3% vs. 14.1%, p=0.03). In the final results (Derdeyn et al. 2014), after a median duration of follow-up period of 32.4 months, fewer patients in the medical group had a primary endpoint event (15% vs. 23%) and the cumulative probability of the primary endpoints was significantly smaller in the medical group (p=0.0252). A similar trial, Vitesse Stent Ischemic Therapy (VISSIT) was halted after the recruitment of 112 patients, when the negative results from the SAMMPRIS trial became available (Zaidat et al. 2015). Among patients who had been randomized up to that point, the 1-year primary outcome occurred significantly more frequently in patients in the

stenting group (36.2% vs. 15.1%, mean difference=21.1%, 95% CI 5.4-36.8%, p=0.02). The risk of stroke recurrence (but not TIA) within one year was also significantly higher in the stenting group (34.5 vs. 9.4%, mean difference 25.1%, 95% CI 10.5-39.6%, p=0.003). More recently, the SPACE-2 trail (Reiff et al. 2019), reported there were no deaths or myocardial infarctions (MI) in any of the study groups (best medical management, CEA and CAS) within 30 days, or in ipsilateral stroke at one year.

Carotid Artery Stenting vs. Carotid Endarterectomy

The risk of periprocedural death and stroke have been shown to be higher following CAS procedures compared with CEA. Zhang et al. (2015) included the results from 35 studies comparing CEA and CAS. Overall, the risk of the primary outcome (stroke or death within 30 days) was significantly higher with CAS (RR=1.51, 95% CI 1.32-1.74, p<0.001). The risk of any stroke or death did not differ significantly between groups at 2 or 3-year follow-up; however, the risk was significantly increased at 4- and 10-years' follow-up for CAS-treated patients (RR=1.24, 95% CI 1.04-1.46, p=0.01 and RR=2.27, 95% CI 1.39-3.71, p=0.001, respectively). Brott et al. (2019) included the results from 4 RCTs (EVA-3S, SPACE, ICSS and CREST), and reported the risk of stroke or death was increased significantly during the periprocedural and post-procedural periods in the CAS group (11.4% vs. 8.3%; HR=1·45, 95% CI 1·20 to 1·75). The risk difference in the outcome of stroke or death between CEA and CAS favoured the CEA group at 1 year (3.1%), 3 years (2.8%), 5 years (3.0%), 7 years (3.7%) and 9 years (4.1%) after randomization. A recent Cochrane review (Müller et al. 2020) included the results of 22 trials of patients with symptomatic stenosis, who had experienced a minor stroke, those with asymptomatic stenosis or both asymptomatic and symptomatic carotid stenosis. The treatment contrasts included any CEA procedure vs. any endovascular technique (primarily stenting +/- protection devices). Among patients with symptomatic stenosis, stenting was associated with a higher risk of death or any stroke within 30 days of treatment (OR=1.70, 95% CI 1.31- 2.19). In pre-planned subgroup analysis, using data from 6 trials, the risk of periprocedural death or stroke did not differ significantly between stenting and CEA in patients <70 years (OR=1.11, 95% CI 0.74 to 1.64), but was significantly higher in patients ≥70 years treated with stenting (OR=2.23, 95% CI 1.61 to 3.08). The risk of death or any stroke between randomization and 30 days after treatment or ipsilateral stroke until the end of follow-up was also higher in the stenting group. Among patients with asymptomatic stenosis, the risk of death or any stroke within 30 days of treatment was also significantly higher in those who received a stenting procedure compared with CEA (RR=1.72 95% CI 1.00 to 2.97), while there was no significant difference between groups for the other primary or secondary outcomes. The authors suggested that for patients with symptomatic stenosis, the combined procedural safety and long-term efficacy profile favours CEA, while in patients with asymptomatic carotid stenosis, there may be a small increase in the risk of stroke or death within 30 days of treatment associated with stenting, but further trials are necessary to provide additional data.

The Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy (SPACE) Trial included 1,200 patients, with symptomatic carotid artery stenosis, who had experienced TIA or moderate stroke within 180 days and with severe carotid artery stenosis (≥ 50% according to NASCET) (Ringleb et al. 2006). Patients were randomized to receive CAS (27% used embolic protection devices) or CEA after a median delay of 4-5 days. The trial was stopped prematurely due to concerns regarding funding and futility. There were no differences between groups on either any of the primary outcomes of 30-day ipsilateral stroke or death, or any of the secondary outcomes (disabling stroke or death from any cause within 30 days, disabling stroke, or procedural failures). The Asymptomatic Carotid Trial (ACT 1) (Rosenfield et al. 2016), a noninferiority trial was stopped early due to slow enrolment. While the protocol aimed to recruit 1,658 patients, data from only 328 patients were available for follow-up assessment at 5 years. At one year, the occurrence of the primary outcome (composite of death, stroke, or myocardial infarction within 30 days of the procedure or ipsilateral stroke within 1 year of the procedure) was 3.8% for stenting group compared with 3.4% for CEA group. The threshold of a 3%-point difference for inferiority was not exceeded (upper 95% CI for difference was 2.27%), suggesting that CAS was not inferior to endarterectomy. Survival from 30 days to 5 years was not significantly different between groups (87.1% stenting group vs. 89.4% CEA group, p=0.21).

The International Carotid Stenting Study (ICSS) trial enrolled 1,713 patients >40 years, with

symptomatic carotid artery stenosis ≥50% using the NASCET criteria (Ederle et al. 2010). Between randomization and 120 days, stenting was associated with an increased risk of stroke, death or procedural myocardial infarction, (8.5% vs. 5.2%, HR=1.69, 95% CI 1.16-2.45, p=0.006) any stroke (7.7% vs. 4.1%, HR=1.92, 95% CI 1.27-2.89, p=0.002), any stroke or death (8.5% vs. 4.7%, HR=1.86, 95% CI 1.26-2.74, p=0.001) and all-cause mortality (2.3% vs. 0.8%, HR=2.76, 95% CI 1.16-6.56, p=0.017). In the long-term study analysis Bonati et al. (2015) reported that after a median duration of 4.2 years the risk of any stroke was significantly increased in the stenting group (HR=1.71, 95% CI 1.28 -2.3, p=0.0003), while stenting was not associated with an increased risk of fatal or disabling stroke (HR=1.06, 95% CI 0.72-1.57, p=0.77). There was also a significantly increased risk of the outcome of periprocedural stroke/procedural death or ipsilateral stroke during follow-up (HR=1.72, 95% CI 1.24-2.39, p=0.001).). In both the per protocol and intention-to-treat analyses, the cumulative 5-year stroke risk was significantly higher in the stenting group (HR=1.53, 95% CI 1.02-2.31 and HR=1.71, 95% CI 1.28-2.30, respectively), while the 5-year risk of fatal or disabling stroke was not increased. The distribution of modified Rankin Scores was similar between groups.

The Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST) trial included 2,502 patients with asymptomatic or symptomatic carotid artery stenosis who had experienced a minor stroke or TIA within the previous 180 days (Brott et al. 2010). The primary end point was the composite of any stroke, myocardial infarction, or death during the peri-procedural period or ipsilateral stroke within four years after randomization. There was no significant difference in the estimated four-year rates of the primary end point between groups (7.2% vs. 6.8%); however, the 4-year rate of stroke or death was higher in the stenting group (6.4% vs. 4.7%, HR=1.50, 95% CI 1.05-2.15, p=0.03). During the periprocedural period, there was a significantly increased risk of stroke or death associated with stenting, but no difference in risk for stroke, death or MI between treatment conditions from 31 days to end of follow-up. After the 30-day, periprocedural period, incidence of ipsilateral stroke was similarly low in both groups (2.0 vs. 2.4%, p=0.85). At 10 years, there was no significant difference between groups in the risk of the primary outcome, which included stroke, death or MI (HR=1.10, 95% CI 0.83-1.44, p=0.51), or in the risk of stroke between groups (HR=0.99, 95% CI 0.64-1.52) (Brott et al. 2016).

Timing of Revascularization Procedures

When indicated, revascularization procedures should be performed as soon as possible following minor stroke or TIA; ideally, within 14 days. Without these procedures, the risk of recurrent events is high. Johansson et al. (2013) reported the overall frequency of ipsilateral ischemic stroke recurrence before CEA was 18.6% in the ANSYSCAP study. The frequency of ipsilateral ischemic stroke recurrence was 5.2% within two-days, 7.9% within 7days, and 11.2% within 14 days of the presenting event. Johansson et al. (2016) included 377 patients with symptomatic carotid stenosis (50-99%), who were eligible for CEA or CAS. Of these, 51 patients had an ipsilateral ischemic stroke or retinal artery occlusion within 90 days. The percentage of patients who experienced recurrent events increased with time of delay from event to procedure (1 day, 2.7%; 3 days, 6.6%; 14 days, 11.5%; 30 days, 13.7% and 90 days: 18.8%). The pattern of results was similar for the outcome of disabling or fatal stroke.

Hospital and Operator Volumes

Increasing experience of an operator or hospital has been shown to reduce the number of adverse events. Poorthuis et al. (2019) included the results of 87 studies examining the association between operator or hospital volumes and outcomes after carotid revascularization procedures. The risk of the primary outcome (procedural death or stroke within 90 days) was significantly lower among high-volume operators following both CEA and CAS procedures (CEA: unadjusted RR=0.59, 95% CI 0.42–0.83; 9 cohorts and CAS: unadjusted RR=0.50, 95% CI 0.32–0.79; 1 cohort), although there was wide variability in the descriptions of low and high-volume operators.

Cervical Artery Dissection

While the incidence of cervical artery dissections (CeAD) is relatively low, estimated to be between 2.6

to 2.9 per 100,000, CeAD is over-represented among persons less than 45 years (Weimar et al. 2010). Given the increased risk of recurrent stroke associated with CeAD, treatment with either antiplatelets or anticoagulants for at least 3 months is recommended. Based on the results of the *Cervical Artery Dissection in Stroke (CADISS) Study* (Markus et al. 2015), treatment with either agent appears to be equally effective for the prevention of recurrent stroke. In this trial, 250 patients with extracranial carotid or vertebral artery dissection were randomized, within 7 days of the event, to receive antiplatelet agents (dipyridamole, aspirin or clopidogrel, alone or in combination) or anticoagulant therapy (UFH, LMWH, followed by warfarin, with a target INR of 2-3), for the study duration. At the end of 3 months, the frequency of the primary outcome (stroke or death), was similar between groups. There were 4 recurrent strokes (3 antiplatelet vs. 1 anticoagulant) and no deaths in either group. There was a single case of major bleeding in the anticoagulant group. At one year (Markus et al. 2019), the risks of ipsilateral stroke, ipsilateral stroke or TIA, any stroke or TIA, or any stroke or death were similar between groups in both the intention-to-treat and per-protocol analyses. Among 181 patients who had MRI or CTA imaging performed at baseline and repeated at 3 months, there was no difference in the presence of residual narrowing or occlusion between those receiving antiplatelet therapy (n = 56 of 92) vs those receiving anticoagulant therapy (n = 53 of 89) (p = .97).

Similar findings were reported in a meta-analysis including the results of 34 non-randomized studies examining the same treatment contrast (Menon et al. 2008). There were 13/185 (7.0%) in the antiplatelet group and 17/447 (3.8%) in the anticoagulant group who suffered a TIA or stroke. The risk difference between groups was not significant (5%, 95% CI -1% to 11%, p = 0.11). The use of novel oral anticoagulants (NOAC) for the prevention of recurrent stroke following CAD has not been well studied. There are no RCTs to date. In a retrospective study (Caprio et al. 2014) including 149 patients with CAD, who were prescribed antithrombotic medication at hospital discharge, there were 2 recurrent strokes during a median of 7.5 months follow-up in the NOAC group compared with one each in the anticoagulant (AC) and antiplatelet (AP) groups. There were significantly fewer major hemorrhagic events in the NOAC group (0 vs. 8 [AC] and 1 (AP], p=0.034).

Table 9: **Risk of recurrent stroke among patients with carotid stenosis ≥50% and recent stroke awaiting carotid endarterectomy or carotid stenting.**

Study	Timing from event to procedure	Frequency of recurrent stroke
Johansson et al. 2016 **Pooled analysis (n=377)**	Not reported	The overall frequency of ipsilateral ischemic stroke recurrence or retinal artery occlusion was 13.5% within 90 days of qualifying event. The frequency of recurrent ischemic stroke/RAO was 2.7% at day 1, 5.3% at day 3, 11.5% at day 14, and 18.8% at 90 days.
Johansson et al. 2013 **ANSYSCAP study (n=230)**	0–7 days: 5% 8–14 days: 14% 15–30 days: 34% 31–89 days: 34% ≥90 days: 12%	The overall frequency of ipsilateral ischemic stroke recurrence before CEA was 18.6%. The frequency of ipsilateral ischemic stroke recurrence was 5.2% within two-days, 7.9% within 7days, and 11.2% within 14 days of the presenting event
Marnane et al. 2011 **(n=36 with carotid stenosis)**	Not reported	The frequency of recurrent stroke was 5.6% at 72 hours following symptom onset, 5.6% at 7 days and 8.3% at 14 days. The risk of recurrent stroke was significantly higher in patients with vs. without ipsilateral carotid stenosis at all time points
Ois et al. 2009 **(n=163)**	Not reported	The overall frequency of neurological recurrence defined as new neurological event (transient ischemic attack or stroke) or an increase of 4 points in the initial NIHSS, during the first 2 weeks was 27.6%.

		The frequency of neurological recurrence was 16% during the first 24 hours after admission, 6.7% between 72 hours and 7 days, and 3.7% at 14 days. 20.9% of patients experienced a neurological recurrence within the first 72 hours following stroke

References

Johansson E, Cuadrado-Godia E, Hayden D, Bjellerup J, Ois A, Roquer J, Wester P, Kelly PJ. Recurrent stroke in symptomatic carotid stenosis awaiting revascularization A pooled analysis. Neurology. 2016;86(6):498-504.

Johansson EP, Arnerlöv C, Wester P. Risk of recurrent stroke before carotid endarterectomy: the ANSYSCAP study. International Journal of Stroke. 2013;8(4):220-7.

Marnane M, Chroinin DN, Callaly E, Sheehan OC, Merwick A, Hannon N, Horgan G, Kyne L, Moroney J, McCormack PM, Dolan E. Stroke recurrence within the time window recommended for carotid endarterectomy. Neurology. 2011;77(8):738-43.

Ois A, Cuadrado-Godia E, Rodríguez-Campello A, Jimenez-Conde J, Roquer J. High risk of early neurological recurrence in symptomatic carotid stenosis. Stroke. 2009;40(8):2727-31.

Extracranial Carotid Disease and Intracranial Atherosclerosis Evidence Tables and Reference List

10. Other Cardiac Issues in Individuals with Stroke

Note: These recommendations are applicable to ischemic stroke and/or transient ischemic attack.

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 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

i. Warfarin can reduce recurrent stroke; however, this benefit may be outweighed by the increased risk of major hemorrhage.

ii. 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 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 transient ischemic attack 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 transient ischemic attack 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].

Rationale

Patent Foramen Ovale

For years, the role of percutaneous closure of a patent foramen ovale (PFO) for secondary stroke prevention had been controversial, because (1) PFO is common in the general population (25%), (2) they are most often incidental rather than pathogenic, and (3) the initial RCTs of PFO closure versus medical therapy were inconclusive. In 2017 and 2018, the publication of three new RCTs and long-term follow-up of an earlier one, demonstrated that among carefully selected patients PFO closure was superior to medical therapy for prevention of stroke recurrence (Saver JL, et al. Stroke 2018;49:1541-8). Meta-analyses of the PFO trials (Mir H et al. BMJ Open 2018;8:e023761; Kent DM et al. J Am Coll Cardiol 2016;67:907-17; Stortecky et al. Eur Heart J 2015;36:120-8) support PFO closure for carefully selected patients aged 60 years or younger with an unexplained embolic stroke event who are found to have a PFO and who do not require chronic anticoagulant therapy for another reason. PFO is not recommended for patients whose PFO is most likely incidental rather than causal for the index stroke event. In such circumstances, antiplatelet therapy alone is recommended for secondary stroke prevention, unless there is a separate evidence-based indication for anticoagulant therapy. None of the PFO trials (except one) enrolled patients over age 60 years. Therefore, based on the available trial evidence, PFO closure cannot be recommended for elderly patients with stroke. PFO closure is not recommended for primary stroke prevention.

The recommendation for PFO closure places high value on avoidance of disabling ischemic stroke, especially for young patients with a long-life expectancy, and avoidance of bleeding complications associated with long-term anticoagulant therapy. The recommendation places less value on the fact that a PFO is associated with a relatively low annual absolute risk of stroke recurrence (1.2% per year), there is often uncertainty regarding whether or not the PFO was truly the causal factor, the fact that PFO closure can only prevent PFO-related strokes, and in a minority of cases PFO closure is incomplete leaving a residual shunt. While the annual absolute risk reduction associated with PFO closure is small, the long-term benefit over decades for young patients may become quite large. Patient counselling and shared decision-making, taking into account patient values and preferences, are encouraged and decision aids have been developed (MAGICapp: Patent foramen ovale closure, antiplatelet therapy or anticoagulation therapy for management of cryptogenic stroke; available at: https://app.magicapp.org/#/guideline/2649). Patients considering PFO closure need to understand the benefits and risks of the procedure and the alternatives and accept an up-front risk of procedural complications that is relatively small but potentially serious, including atrial fibrillation. In the meta-analysis by Mir et al., the overall incidence of procedural complications was 3.6%, and there was an 1.8% absolute increase in the risk of persistent atrial fibrillation and a 1.2% increase in the risk of transient atrial fibrillation (Mir H et al. BMJ Open 2018;8:e023761).

When PFO closure is being contemplated, careful patient selection is essential. The committee advocates consultation with a stroke specialist and an experienced interventional cardiologist with a low rate of procedural complications. A consensus statement on technical standards for operators has been published (Horlick et al. Catheter Cardiovasc Interv 2019;93:859-874). The appropriateness of PFO closure depends on (1) an accurate diagnosis of the index stroke event and exclusion of mimics, and (2) a thorough etiological workup to exclude alternate more likely causes for the stroke event. Given that transient ischemic attack can be difficult to diagnose (over-diagnosis of transient ischemic

attack is a common problem in clinical practice because many conditions may mimic a transient ischemic attack), and the fact that patients none of the PFO trials (except for one) enrolled patients with transient ischemic attack as the index event, the committee had concerns about the potential for inappropriate PFO closure procedures for patients with transient ischemic attack mimics. Therefore, transient ischemic attack was removed from the general recommendations above regarding PFO closure. If PFO closure is offered to a patient with transient ischemic attack, the transient ischemic attack diagnosis should be convincing, i.e., a high degree of certainty that the index event was a genuine cerebral ischemic event, ideally with cortical symptoms and verified by a neurologist; every effort should be made to obtain brain imaging evidence for confirmation of acute embolic ischemia.

Heart Failure

In patients with ischemic stroke or transient ischemic attack who have either left atrial or left ventricular thrombus, anticoagulant therapy with VKA is recommended for ≥ 3 months (Level of Evidence C). [13] In the WARCEF randomized trial of 2305 patients with heart failure (left ventricular function ≤35%) and in sinus rhythm, warfarin reduced the risk of ischemic stroke but the benefit was offset by an increase in major bleeding. In a meta-analysis of patients with congestive heart failure with reduced ejection fraction, warfarin was compared with antiplatelet therapy and there was a small absolute reduction in the risk of ischemic stroke in those treated with warfarin, but this was accompanied by an increased risk of major hemorrhage (mostly intracranial hemorrhage), and was not associated with any accompanying reduction in death, MI, or hospitalization due to heart failure. In the COMMANDER HF trial of patients with reduced left ventricular ejection fraction (40%) in sinus rhythm, rivaroxaban at a dose of 2.5mg twice daily was not associated with a significantly lower rate of the composite outcome of death, MI or stroke compared with placebo, although stroke events were reduced.

People with stroke, their family and caregivers expressed the desire to learn more about the connection between the heart and the brain. Many people with stroke were not aware of the conditions discussed in this section, such as a PFO, and the potential connections to stroke. Some people with stroke did not know if they had been investigated for these conditions and if they were, what the results where.

People who have experienced a stroke and have concurrent heart conditions have described the challenges of siloed healthcare systems on their care. For example, some health professionals only wanted to focus on their stroke related conditions and would not discuss other factors, such as heart conditions. In addition, there have been experiences of inconsistent information sharing between specialties and an opportunity for more integrated and coordinated care for people with a broader range of vascular risk factors affecting both heart and brain.

System Implications

1. Integration of care for people with heart and stroke conditions to efficiently manage appointments and ensure coordination of care.
2. Support for ongoing research into etiology for patients with cryptogenic stroke.
3. Support for research to further investigate the impact of PFO closure versus medical therapy.

Performance Measures

1. Proportion of people who experience an acute stroke who have a patent foramen ovale.
2. Proportion of people with acute ischemic stroke and PFO who are treated with antiplatelet agents or anticoagulants (and specific type of anticoagulant – LMWH, warfarin or DOAC).
3. Proportion of people with acute ischemic stroke and PFO who undergo a PFO closure procedure.
4. Median time from stroke to PFO closure.
5. Proportion of people who experience an acute stroke who also have a diagnosis of heart failure.
6. Median time from diagnosis of heart failure to stroke event.

7. Mortality rates for people with pre-existing heart failure who experience an acute stroke (stratified by ischemic or hemorrhage).

Measurement Notes:

- All performance measures should be stratified by age, sex, type of stroke and time from heart diagnosis to stroke occurrence.
- PFO may only be detected after a stroke has occurred.

Implementation Resources and Knowledge Transfer Tools

Health Care Provider Information

- Heart & Stroke: Post-Stroke Checklist:
  https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/002-17_csbp_post_stroke_checklist_85x11_en_v1
- Heart & Stroke: Your Stroke Journey:
  https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/en-your-stroke-journey-v21
- Heart & Stroke: Online and Peer Support
  https://www.heartandstroke.ca/heart-disease/recovery-and-support/the-power-of-community
- Thrombosis Canada
  http://thrombosiscanada.ca/?resourcepage=resources-2
- Canadian Cardiovascular Society
  https://ccs.ca/guidelines-and-position-statement-library/

  Canadian Heart Failure Society: https://heartfailure.ca/
- Canadian Cardiovascular Harmonized National Guidelines Endeavour (C-CHANGE): guideline for the prevention and management of cardiovascular disease in primary care: 2018 update:
  https://www.cchangeguidelines.com/copy-of-guidelines-2

  Canadian Cardiovascular Harmonized National Guidelines Endeavour (C-CHANGE) guideline for the prevention and management of cardiovascular disease in primary care: 2018 update | CMAJ

Patient Information

- Heart & Stroke: Post-Stroke Checklist:
  https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/002-17_csbp_post_stroke_checklist_85x11_en_v1
- Heart & Stroke: Online and Peer Support https://www.heartandstroke.ca/heart-disease/recovery-and-support/the-power-of-community
- Heart & Stroke: Heart Conditions Resource:
  https://www.heartandstroke.ca/heart-disease/conditions
- Heart & Stroke: Working with your doctor:
  www.heartandstroke.ca/heart-disease/recovery-and-support/working-with-your-doctor
- Heart & Stroke Patent Foramen Ovale:
  https://www.heart.org/en/health-topics/congenital-heart-defects/about-congenital-heart-defects/patent-foramen-ovale-pfo
- Heart & Stroke: Living Well With Heart Disease:
  https://www.heartandstroke.ca/-/media/pdf-files/canada/2017-lwwhd/livingwellwheartdisease-en

- Heart & Stroke: Living With Heart Failure https://www.heartandstroke.ca/-/media/pdf-files/canada/health-information-catalogue/en-living-with-heart-failure
- HeartLife: https://heartlife.ca/
- Canadian Heart Failure Society: Patient Resources: https://heartfailure.ca/education/patient-resources

Summary of the Evidence 2020

Patent foramen ovale (PFO)

Three earlier RCTs, CLOSURE 1 (Furlan et al. 2012), the PC Trial (Meier et al. 2013), and RESPECT (Carroll et al. 2013) investigated the effectiveness of PFO closure for reducing the risk of stroke recurrence and mortality following cryptogenic stroke, compared to medical management. Across the three trials, no significant reductions in the risk of the primary outcomes, which included recurrent stroke or transient ischemic attack and death, were associated with closure in their respective intention-to-treat analyses. The associated hazard ratios (HR were: 0.78 (95% CI 0.45 to 1.35, p=0.37) in CLOSURE 1, during 2-years follow-up; 0.63, (95% CI 0.24 to 1.62, p=0.34) in the PC trial after a mean of 4.1 years of follow-up, and 0.49, (95% CI 0.22 to 1.11, p=0.08) in RESPECT after a mean follow-up of 2.6 years. Whereas the authors of CLOSURE 1 and the PC trials both observed similar findings in per protocol-based analyses, the authors of RESPECT reported that in a per protocol analysis, PFO closure was associated with a significant reduction in the composite outcome of recurrent ischemic stroke or death, compared to medical therapy (HR= 0.37, 95% CI 0.14 to 0.96, p=0.03). There was no significant increase in the risk of serious adverse events in the intervention arm of any of the trials.

Results from recent trials including CLOSE (Mas et al. 2017), REDUCE (Sondergaard et al. 2017), DEFENSE-PFO (Lee et al. 2018), and long-term results of the RESPECT trial (Saver et al. 2017), have demonstrated that among carefully selected patients PFO closure is superior to medical therapy for prevention of stroke recurrence.

In the CLOSE trial, Mas et al. (2017) enrolled 633 patients aged 16–60 years (mean age approximately 43 years) who had experienced a recent stroke with no identifiable cause other than a PFO, following detailed etiological work- up by a neurologist. The PFO had to be associated with either an atrial septal aneurysm (excursion >10 mm) or large interatrial shunt (>30 microbubbles in the left atrium within three cardiac cycles after opacification of the right atrium). Mean duration of follow-up was 5.3±2.0 years. The rate of recurrent stroke was 0 in the PFO-closure group compared with 6.0% in the antiplatelet-only group (mostly aspirin) (HR= 0.03; 95% CI 0-0.26; p<0.001; NNT=20 to prevent 1 stroke in 5 years; 95% CI 17-25). The rate of procedural complications in the PFO closure group was 5.9%, mostly consisting of atrial fibrillation (4.6% in the closure group vs. 0.9% in the antiplatelet group, p=0.02); most cases of atrial fibrillation were transient and did not recur during follow-up.

The REDUCE trial (Sondergaard et al. 2017) enrolled 664 patients aged 18–59 years (mean age 45.2 years) with a PFO with a right-to-left shunt (spontaneous or during Valsalva maneuver), of whom 81% had moderate (6-25 microbubbles) or large (>25 microbubbles) interatrial shunts. Median follow-up was 3.2 years. The risk of ischemic stroke was significantly lower in the PFO closure group compared with the antiplatelet-only group (1.4% vs. 5.4%, HR=0.23, 95% CI 0.09-0.62; p=0.002; NNT=28 to prevent 1 stroke in 2 years). Serious device-related adverse events occurred in 1.4% of patients. The frequency of new-onset atrial fibrillation or flutter was significantly higher in the PFO closure group (6.6% vs 0.4%, p<0.01); most cases of atrial fibrillation in the closure group were transient.

The RESPECT trial enrolled patients aged 18–60 years (mean age 45.9 years) with a cryptogenic stroke and PFO. In the extended follow-up analysis, during a median duration of follow-up of 5.9 years, the risk of recurrent ischemic stroke was significantly lower in the PFO closure group compared with the medical therapy group (antiplatelet therapy or warfarin) (3.6% vs. 5.8%; HR=0.55, 95% CI 0.31-0.999, p=0.046, NNT=42 to prevent 1 stroke in 5 years). In subgroup analysis, the benefit of closure appeared to be driven by those with an atrial septal aneurysm or a “substantial” shunt size (grade 3).

Lee et al. (2018) randomized 120 patients aged 18-80 years, with a cryptogenic ischemic stroke occurring within the previous 6 months with no identifiable cause other than a high risk PFO with right-to-left shunting to receive medical therapy with antiplatelet or anticoagulation alone, or PFO closure. Antiplatelet therapy included aspirin (100 mg/day), aspirin in combination with clopidogrel (75 mg/day), or aspirin in combination with cilostazol (200 mg/day). Dual antiplatelet therapy was used by most patients in both groups at 30 days and 6 months. At 12 months, more patients in the PFO group were taking a single antiplatelet, compared with the medical therapy group. Anticoagulants were used by ≤25% of patients at any assessment point. There were significantly more primary outcome events (recurrent stroke and major bleeding within 2 years) in the medication-only group (6 vs. 0, p=0.013), of which 5 were ischemic strokes. The authors estimated that the NNT to avoid one stroke at 2 years, was 10.

Clinical clues to the diagnosis of a PFO-related stroke event include stroke symptom onset preceded by a Valsalva maneuver, waking up with a stroke, sleep apnea, deep vein thrombosis or pulmonary embolism, respiratory symptoms at the time of stroke onset, and recent prolonged travel or immobilization (Ozdemir AO et al. J Neurol Sci 2008;275:121-7). History-taking should elicit whether there is a personal or family history of venous thromboembolism or high-risk thrombophilia. The Risk of Paradoxical Embolism (RoPE) score can help higher scores (younger age, cortical infarct, and absence of traditional vascular risk factors) predict that a PFO is more likely to be stroke-related than incidental (Kent DM et al. Neurology 2013;81:619-625).

There have been conflicting data on the significance of PFO size and uncertainty whether or not an isolated small PFO/small shunt without an atrial septal aneurysm should be closed. In meta-analysis of the PFO trials, the benefit of PFO closure over medical therapy was maximal in subgroups with a large PFO or substantial shunt or atrial septal aneurysm; in subgroups without any of those anatomical features, a significant benefit of PFO closure was not observed (Mas J-L et al. Archives of Cardiovascular Disease 2019;112:532-542; Turc G et al. J Am Heart Assoc 2018;7; Pristipino C et al. European Heart Journal 2018; Saver JL, et al. Stroke 2018;49:1541-8). However, it has been pointed out that the observed effect of shunt size may be confounded by a higher proportion of antiplatelet therapy rather than anticoagulation in the medical arms of the trials that enrolled more patients with larger shunts (Mir H et al. BMJ Open 2018;8: e023761). According to Saver et al., the NNT to prevent 1 stroke over 5 years with PFO closure plus antiplatelet therapy (versus antiplatelet therapy alone) is 24 overall. For PFO closure versus medical therapy, the NNT to prevent 1 stroke in 5 years is lower among patients with an atrial septal aneurysm (NNT=13) and among patients with moderate-large shunts (NNT=18) (Saver JL, et al. Stroke 2018;49:1541-8).

There remains uncertainty about the relative effectiveness of anticoagulant therapy versus antiplatelet therapy for patients with a stroke and PFO (without atrial fibrillation) who do not undergo PFO closure. In the PFO subgroup analyses from the ESUS trials, there was a (non-significant) trend in favour of DOAC therapy over aspirin in the NAVIGATE ESUS trial (Kasner SE et al. Lancet Neurol 2018;17:1053-1060) but not in the RESPECT ESUS trial (Diener HC et al. NEJM 2019;380:1906-1917). In the CLOSE trial, there were numerically fewer recurrent stroke events among patients assigned to the anticoagulation arm (in which 93% received a vitamin K antagonist and 7% received a DOAC) compared with the antiplatelet arm, but this comparison was underpowered. An updated meta-analysis of 5 trials found a non-significant trend in favour of anticoagulation over antiplatelet therapy (Sagris D, et al. Stroke 2019;50). Anticoagulation has the advantage of providing protection against both arterial and venous thromboembolic events beyond the PFO, and hence would probably be preferred for patients with unprovoked deep vein thrombosis or pulmonary embolism or a high-risk thrombophilia.

When the results of 6 RCTs (CLOSURE, PC, RESPECT, GORE-Reduce, CLOSE and DEFENSE PFO) were pooled (Turc et al. 2018), the risk of recurrent stroke is significantly lower in the PFO group, compared with antithrombotic therapy (37/1,889 vs. 79/1,671; RR= 0.36, 95% CI 0.17-0.79, p=0.01).

Sex and Gender Considerations: In a single centre study including patients admitted for recent ischemic stroke and referred for transesophageal echocardiography (TEE), the prevalence of PFO was similar in men and women (32.4% vs. 28.2%, p= 0.15, respectively). (Gupta et al. 2008). In a pooled analysis of 5 RCTs, the risk of recurrent stroke was significantly lower in men who had undergone PFO

closure compared with medical management (OR=0.32, 95% CI=0.14–0.73, p=0.01), but was not in women (OR=0.84, 95% CI=0.47–1.51, p=0.56) (Agasthi et al. 2019).

Aortic Arch Atheroma

The definitive management of patients with aortic arch plaques is unclear. Typically, monotherapy with an antiplatelet agent or oral anticoagulation is used to prevent further events in patients with a prior ischemic stroke. Amarenco et al. (2014) tested the hypothesis that dual antiplatelet therapy would be superior to oral anticoagulation. The Aortic Arch Related Cerebral Hazard Trial (ARCH) included 351 patients with a previous ischemic stroke, transient ischemic attack, or peripheral embolism with plaque in the thoracic aorta >4 mm and no other identified embolic source. Patients were randomized to receive 75 to 150 mg/d aspirin + 75 mg/d clopidogrel or dose-adjusted warfarin with a target INR of 2.5 (2-3) for the duration of the trial. After a median of 3.4 years of follow-up, the risk of the primary outcome, a composite of cerebral infarction, myocardial infarction, peripheral embolism, vascular death, or intracranial hemorrhage was not significantly lower in the dual therapy group (7.6% vs. 11.3%, HR=0.76, 95% CI 0.36-1.61, p=0.50). There was no significant difference in the occurrence of major hemorrhages between groups (2.3% for dual therapy vs. 3.4% for warfarin, p=0.2).

Risk of Recurrent Stroke Associated with Heart Failure

Heart failure is known to be associated with increased risk of recurrent stroke. Katsanos et al. (2016) included the results from 7 studies (n=9,173) that reported the recurrence of ischemic stroke in patients with heart failure. The definitions used for heart failure were based on medical history (n=3), ejection fraction (n=1), Framingham criteria (n=1) or were not reported (n=3). Within the included studies, the percentage of patients with heart failure ranged from 4.8% to 33.9%. The mean follow-up durations across the included studies ranged from 7 days to 5 years. The risk of recurrent stroke was significantly increased among patients with heart failure (RR=1.96, 95% CI 1.49 -2.60, p<0.0001). Using data from the Canadian Stroke Registry, Pongmoragot et al. (2016) compared the outcomes of 12,396 patients admitted to hospital following an ischemic stroke with heart failure versus those without. Heart failure was defined either as pre-existing, or pulmonary edema present at the time of arrival to hospital. While the number of patients with stroke recurrence at 30 days did not differ between groups (3.9% vs. 3.2%, p=0.194), stroke fatality at discharge, 30 days and 1 year was significantly higher for patients with heart failure. Heart failure was also an independent predictor of death or disability at discharge (OR=1.18, 95% CI 1.01-1.37), 30-day survival (HR=1.22, 95% CI 1.05-1.41) and 30-day readmission (OR=1.32, 95% CI 1.05-1.65), after adjusting for age, sex, stroke severity and medical comorbidities.

Stroke Prevention for Patients in Heart Failure

The effectiveness of anticoagulation compared with antiplatelet therapy for stroke prevention in patients with heart failure in sinus rhythm remains unclear. Although several trials have compared their relative effectiveness, the superiority of any one approach has not been demonstrated. Most recently, the COMMANDER-HF trial (Zannad et al. 2018) randomized 5,081 participants in sinus rhythm with chronic heart failure, a left ventricular ejection fraction (LVEF) of ≤40%, with coronary artery disease and who had been treated for an episode of worsening heart failure within the previous 21 days, to receive 2.5 mg rivaroxaban twice daily or matching placebo in addition to standard care (including mono or dual antiplatelet therapy). After a median of 21.1 months, there was no difference between groups in the risk of the primary composite outcome of death from any cause, MI, or stroke (rivaroxaban 13.44 events/100 persons years vs. placebo 14.27 events/100-person years; HR=0.94, 95% CI 0.84–1.05, p=0.27), although the risk of stroke was reduced significantly in the rivaroxaban group (1.08 vs. 1.63 events/100-person years; HR=0.66, 95% CI 0.47–0.95).

The Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial included 2,305 patients with LVEF ≤35% (Homma et al. 2012). Patients were randomized to receive 325 mg aspirin daily or warfarin with a target INR of 2.75 for the study duration. After an average of 3.5 years, the rates for the primary outcome, a composite outcome of time to first event of ischemic stroke,

intracerebral hemorrhage or death from any cause, were similar between groups (7.47 and 7.93 events/100 patient years for warfarin and aspirin, respectively: HR for warfarin=0.93, 95% CI 0.79-1.10, p=0.40). Although warfarin was associated with a significantly reduced risk of ischemic stroke (HR=0.52, 95% CI 0.33-0.82, p=0.005), the risks of major and minor hemorrhages were significantly increased. A subgroup analysis of the WARCEF trial (Homma et al. 2013) found that patients <60 years treated with warfarin had a significantly lower risk of the primary outcome (HR=0.63, 95% CI 0.48-0.84, p=0.003) compared with aspirin therapy, while there was no significant treatment effect for patients 60 years or older. Patients <60 years treated with warfarin had a significantly lower risk of the primary outcome plus any major hemorrhage (HR=0.68, 95% CI 0.52-0.89, p=0.005). Patients ≥60 years treated with warfarin had a higher risk (HR=1.25, 95% CI 1.02-1.53, p=0.03) compared with aspirin. Investigators of the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) Trial compared 162 mg aspirin daily versus 75 mg clopidogrel daily versus warfarin, with target INR of 2.5 to 3.0 in patients in heart failure with a LVEF ≤35% (Massie et al. 2009). The risk of the primary outcome was similar between groups (20.7% aspirin vs. 21.6% clopidogrel vs. 19.6% warfarin). While warfarin was associated with a decreased risk of nonfatal and total stroke compared with either antiplatelet agent, the risk of bleeding events was significantly higher among patients in the warfarin group compared with clopidogrel.

Cardiac Issues and Stroke Evidence Tables and Reference List

*Section 11: Cancer-Associated Ischemic Stroke ** NEW Section for 2020 **

Section 11 Recommendations

11.1 Cancer-Associated Ischemic Stroke

i. Patients with active malignancy who experience an arterial ischemic stroke or transient ischemic attack should undergo a standard etiological work-up for their stroke, including vascular imaging and cardiac rhythm monitoring [Evidence Level C]. *Refer to Section 1on 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 transient ischemic attack 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 direct oral anticoagulants is unknown but under study and may be reasonable after consideration of patient preference.

Section 11 Clinical considerations

i. 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.

ii. In patients with active malignancy and arterial ischemic stroke or transient ischemic attack with a concurrent venous thromboembolism (deep vein thrombosis or pulmonary embolism) 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 low molecular weight heparin (LMWH) and selected DOACs (Refer to www.thrombosiscanada.ca).

Rationale

A diagnosis of cancer can increase the risk of stroke. This has been found to occur across time following a diagnosis of cancer, and has occurred more frequently in persons with brain, lung or gastrointestinal tract cancer, or with more advanced cancers. Stroke may be a result of traditional cardiovascular risk factors, as well as cancer-mediated factors including hypercoagulability, non-bacterial thrombotic endocarditis (NBTE), direct tumor compression of blood vessels, or treatment-related effects which potentiate stroke. With increasing survival rates from cancer, there is a greater need to assess stroke risk and to optimize stroke prevention strategies. The risk of stroke among cancer patients is two times that of the general population and rises with longer follow-up time (Zaorsky et al, Nature Communications, 2019).

System Implications

1. Integrated systems of care for people with cancer and stroke to efficiently manage appointments and ensure coordination of care and safety with respect to medication and treatment options.
2. Support for ongoing research into the relationship between cancer and stroke.
3. Awareness and education efforts for health professionals and the public

Performance Measures

1. Proportion of people who experience an acute stroke who also have a diagnosis of cancer.
2. Median time from diagnosis of cancer to stroke event.
3. Proportion of people with stroke and cancer with elevated serum biomarkers such as high D-Dimer levels and fibrin degradation products.
4. Proportion of people with acute ischemic stroke and previous cancer diagnosis who receive intravenous thrombolysis and or endovascular treatment.
5. Proportion of people with acute ischemic stroke and previous cancer diagnosis who are treated with antiplatelet agents (or anticoagulants (and specific type of anticoagulant – LMWH, warfarin or DOAC).
6. Mortality rates for people with pre-existing cancer who experience an acute stroke (stratified by ischemic or hemorrhage).
7. Proportion of people with pre-existing cancer who experience an acute stroke (stratified by ischemic or hemorrhage) who have a recurrent stroke within 90 days, 6 months or one year of index stroke.

Reference: Dardiotis et al, Int J Oncol. 2019 Mar; 54(3): 779–796. Published online 2019Jan02 Jan2. doi: 10.3892/ijo.2019.4669

Measurement Notes:

- Performance measures should be stratified by the type of cancer and treatment approaches (e.g., recent chemotherapy, radiation or surgery).
-

Implementation Resources and Knowledge Transfer Tools

Health Care Provider Information

- Heart & Stroke: Post-Stroke Checklist: https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/002-17_csbp_post_stroke_checklist_85x11_en_v1
- Canadian Cancer Society: https://www.cancer.ca/en/?region=on

Patient Information

- Heart & Stroke: Post-Stroke Checklist: https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/002-17_csbp_post_stroke_checklist_85x11_en_v1
- Heart & Stroke: Your Stroke Journey: https://www.heartandstroke.ca/-/media/1-stroke-best-practices/resources/patient-resources/en-your-stroke-journey-v21
- Heart & Stroke: Online and Peer Support https://www.heartandstroke.ca/heart-disease/recovery-and-support/the-power-of-community
- Canadian Cancer Society: https://www.cancer.ca/en/?region=on

Summary of the Evidence 2020

Increased Risk of Stroke Associated with Cancer

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 (Navi et al. 2017). In a case-control study including 327,389 persons >66 years, with newly diagnosed breast, colorectal, lung, pancreatic, or prostate cancer shorter term, the cumulative 3-month incidence of ischemic stroke was significantly higher in all types of cancer patients, except for prostate cancer (Navi et al. 2015). For lung cancer, the risk of any stroke was significantly higher at all follow-up points (<1 month, 1-3 months, 3-6 months, 6-9 months, and 9-12 months). Hazard ratios ranged from 1.63 at 6-9 months to 7.43 at < 1 month after cancer diagnosis. The risk of any stroke was significantly higher at one or more follow-up points for all other cancers, as well. Stroke risk may also be increased long-term following a cancer diagnosis, as well. Jang et al. (2019) studied 20,707 persons sampled from a population database with cancer and 675,594 without cancer. The incidence of stroke in both groups was examined up to 7 years after cancer diagnosis using both the entire sample and propensity-score matching. The mean follow-up duration of cancer group was 69.7 months and 82.7 months in the non-cancer group. The cumulative incidence of any stroke using the entire cohort, was significantly higher in the cancer group (3.43% vs.1.07%), as were the cumulative incidences of ischemic stroke (3.10% vs. 0.91%), hemorrhagic stroke (0.46% vs. 0.21%) and death (22% vs. 2.03%). The risk of incident stroke was significantly higher in the cancer group (HR=1.09, 95% CI 1.00-1.18) using data from the entire cohort and was higher when the propensity-matched data were used (HR=1.13, 95% CI 1.02- 1.26). Additionally, the risk of any and ischemic stroke was significantly higher in persons who received chemotherapy (adj HR= 1.21, 95% CI 1.03–1.41 and adj HR= 1.19, 95% CI 1.01–1.40, respectively). Zöller et al. (2012) reported the standardized incidence ratios (SIR) for ischemic stroke following a cancer diagnosis < 6 months previously was 1.6%, which decreased to 1.1% at ≥10 years. The SIRs for hemorrhagic stroke were higher (2.2% at <6 months, 1.2% at ≥10 years and 1.2% overall). Not only is the risk of incident stroke increased following a cancer diagnosis, the risk of recurrent stroke is also increased. Navi et al. (2014) reported the cumulative prevalence of recurrent ischemic stroke were 7%, 13% and 16% at one, 3 and 6 months among 263 patients with active systemic cancer, with a hospital admission for stroke.

Cancer-related Hypercoagulopathy

Thrombosis is a common complication of malignancy and represents a frequent cause of death in cancer patients with a history of stroke. In the OASIS Cancer study (Lee et al. 2017) included 268 patients admitted to a single hospital with an acute ischemic stroke and active systemic cancer. Routine anticoagulation studies (D-dimer, PT, aPTT, fibrinogen and platelet counts) were conducted to assess possible hypercoagulopathy. During hospitalization, plasma D-dimer level was serially monitored after the start of the anticoagulation treatment. The pre-treatment and post treatment plasma D-dimer levels were divided into quartiles and their independent relationship with overall and 1-year survival was examined. Baseline D-dimer levels in the 4 quartiles (Q) were: Q1: <2.08 µg/mL; (25.1%), Q2: 2.08–9.06 µg/mL (24.7%), Q3: 9.06–23.26 µg/mL (25.5%) and Q4: >23.26 µg/mL (24.7%). When Q3 and Q4 groups were combined, the risks of overall and one-year mortality were increased significantly compared with group 1 (reference), HR=2.19, 95% CI, 1.46–3.31 and 2.70, 95% CI 1.68–4.35, respectively after adjustment for stroke mechanism, age, NIHSS score, primary cancer type, cancer histology (adenocarcinoma vs others), and atrial fibrillation. Among a subgroup of 113 patients in D-dimer groups 3 and 4 who were treated with anticoagulants, D-dimer levels were reduced (median of 8.17 µg/mL). Post-treatment D-dimer level was independently associated with poor 1-year survival (adjusted HR=1.03; 95% CI, 1.01–1.05 per 1 µg/mL increase, p= 0.015) but not with overall survival. After discharge from hospital, a D-dimer level of 3.17 µg/mL was identified as the cut-point, above which the risk of death within one month was increased significantly (OR=1.07, 95% CI, 1.04–1.10 per 1 µg/mL increase, p<0.001). Schwarzbach et al. (2012) also reported mean D-dimer levels were significantly higher in patients with active malignant cancer admitted to a hospital following ischemic stroke compared with persons in an age and sex-matched control group (7.64 vs. 5.36 µg/mL, p<0.05). The prevalence of DVT and PE was significantly higher in patients with cancer (8% vs. 1%, p<0.01) and in patients with cancer with an unidentified and/ or cancer-associated stroke etiology compared with patients with cancer with a definite/ probable stroke

etiology (15% vs. 1%, p<0.01).

Treatment with Antithrombotics

Navi al. (2018) published one of the only RCTs examining the use of antithrombotics in patients with active cancer who had sustained an ischemic stroke within the previous month. Twenty patients were randomized to receive either subcutaneous enoxaparin (1 mg/kg twice daily) or oral aspirin (81-325 mg/d) for 6 months; however, 6 patients in the enoxaparin group crossed over to use aspirin after a median of 6 days. Treatment groups were too small to conduct inferential statistics. One year after enrollment, three patients in the aspirin group had nonfatal gastrointestinal bleeding and one patient had a nonfatal myocardial infarction. In the enoxaparin group, one patient had a nonfatal pulmonary hemorrhage, and one had a fatal recurrent acute ischemic stroke.

Sex and Gender Considerations

No studies were found that address sex differences on this topic.

Cancer-Related Stroke Evidence Tables and Reference List

APPENDIX ONE

Canadian Stroke Best Practice Recommendations
STROKE PREVENTION WRITING GROUP 2020:

Name	Professional Role	Location	Declared Conflicts of Interest
Gladstone, David	Associate Professor, Department of Medicine (Neurology), University of Toronto; Director, Regional Stroke Prevention Clinic, Sunnybrook Health Sciences Centre, Toronto	Ontario	Received a Mid-Career Investigator Award from the Heart and Stroke Foundation. Received a peer-reviewed provincial operating grant from Ontario Genomics; all funds paid to his institution to support the project (no personal fees). Serves as a national co-leader for the Canadian arm of the NINDS-sponsored ARCADIA trial, and local site PI for the NASPAF-ICH and ENRICH-AF trials (with all site fees paid to his institution; no personal fees). Served as PI of the SCREEN-AF trial (uncompensated; trial funded by the Canadian Stroke Prevention Intervention Network (C-SPIN), which is funded by the Canadian Institutes of Health Research [CIHR]). Site Investigator for NAVIGATE ESUS trial and NASPAF-ICH trial (all site fees paid to my institution); Co-Leader of NAVIGATE ESUS atrial myopathy/atrial fibrillation working group (uncompensated)
Poppe, Alexandre Y	MD, CM, FRCPC Clinical Associate Professor, Department of Neuroscience, Centre hospitalier de l'Université de Montréal (CHUM), Montréal	Quebec	Heart and Stroke - Spokesperson Site PI and Site co-investigator: ESCAPE-NA1 (NoNo), NAVIGATE-ESUS (Bayer), RESPECT-ESUS (Boehringer-Ingelheim), POINT (NIH); DSMB for FLOW Support for fellowship program: Servier Research grant support from Stryker
Bourgoin, Aline	RN, BScN, CNN (C) Stroke Prevention Coordinator, Nurse Specialist, Stroke Prevention Clinic Champlain Regional Stroke Network, Ottawa	Ontario	**No conflicts to declare**
Cox, Jafna	MD, FRCPC, FACC Heart and Stroke Foundation of Nova Scotia Endowed Chair in Cardiovascular Outcomes Research; Professor of Medicine and of Community	Nova Scotia	Medical Consultant (received payment): Bayer, HLS Therapeutics, Novartis Lecture Series (received payment): Bayer Investigator-initiated grant from Bayer Participating in a Phase II study of a Factor

	Health and Epidemiology, Dalhousie University, Halifax * Appointed as rep by Canadian Cardiovascular Society		XI inhibitor, funded by Bayer
Douketis, James	MD, FRCPC(C), FACP, FCCP Vascular Medicine Research, Professor of Medicine, McMaster University, Hamilton	Ontario	Advisory Board Consultant: BMS Pfizer, Servier, Leo Pharma, Sanofi, Bayer. Grant/Honorarium from Thrombosis Canada (non-profit) Participation in PAUSE trial Personal fees - Monies received as personal fees are deposited in hospital based (St. Joseph's Healthcare Hamilton) and university-based (McMaster University) research accounts and/or charitable foundations: Janssen, Pfizer, Bayer, Bristol Myers Squibb, Sanofi, Servier Canada, Portola
Falconer, John B.	MD, FRCPC Neurology President Section of Neurology, BC Clinical Associate Professor of Medicine; Division of Neurology UBC, Kelowna	British Columbia	**No conflicts to declare**
Graham, Brett R.	Adult Stroke Neurologist, Saskatchewan Health Authority Assistant Professor, University of Saskatchewan, Saskatoon	Saskatchewan	Canadian Stroke Consortium - Catalytic Research Capacity Generation Grant University of British Columbia, University of Calgary - SECRET and TOPSECRET site PI, TEMPO-2 an ESCAPE NA1 site sub-I. Honorarium - Servier Canada (to give a talk on anticoagulation in afib to family physicians.)
Heran, Manraj K.S.	MD, FRCPC Associate Professor Division of Neuroradiology Director, Interventional Neuroradiology Fellowship Program Vancouver General Hospital University of British Columbia	British Columbia	No conflicts to declare
Labrie, Marilyn	Neurology, Laval University Stroke Neurology, Hôtel-Dieu de Lévis, Quebec City	Québec	Advisory board member: Teva Canada – Fremanezumab 2020-08-23
Lavoie, Pascale	Neurosurgeon, Assistant Professor, Department of Surgery, Laval University; Hôpital de	Québec	Investments: Johnson and Johnson/United heath group Patient recruitment: Escape NA-1 trial

	l'Enfant-Jésus		
MacDonald, Lena	MN, NP Heart Health Clinic St. Martha's Regional Hospital, Antigonish	Nova Scotia	No conflicts to declare
Mandzia, Jennifer	MD, PhD, FRCPC Assistant Professor, Department of Clinical Neurological Sciences, Western University, London	Ontario	Advisory board with commercial organization – Bayer Clinical trial – Site PI for several studies
Ngui, Daniel	BScPT, MD, FCFP, Clinical Associate Professor, UBC Dept of Family Medicine, Medical Director Fraser Street Medical, Vancouver	British Columbia	Speakers Bureau/Honoraria/Consultancy Advisory Board: Amgen, Astra Zeneca, BMS, BI, Lilly, Novonordisk Moderating and speaking engagements: Amgen, Astra Zeneca, BMS, BI, Lilly, Novonordisk EMR grants and audits: Amgen, Astra Zeneca, BI, Novartis Research Grants: Simple Trial, Amgen 20170191 trial, IHE eCare CV Risk , CHRC EMR Registry Trials: AF OAC, Advantage CV, and Advantage OP-Phase 4 and EMR audits Health Choices First Video Education shares Investments in communications companies: CHRC, CCRN, MD Briefcase, Medplan, Liv Agency, Four Health Board membership – CCS Lipid CPG Panel, CCS A. fib CPG 2nd Panel, SPH Hospital CME Committee, BC Guidelines, UBC CPD CME "This changed my practice", Alliance for Best Practices in Health Education
Pageau, Paul	Emergency Physician, The Ottawa Hospital Assistant Professor, Department of Emergency Medicine, The University of Ottawa, Ottawa	Ontario	No conflicts to declare
Rodgerson, Amanda	B.S.C., RD Clinical Dietician, Provincial Acute Stroke Unit and Provincial Rehabilitation Unit, Queen Elizabeth Hospital, Charlottetown	Prince Edward Island	No conflicts to declare

Semchuk, William	M.Sc., Pharm. D., FCSHP Director Patient care and Performance Support, Pharmacy Services, Saskatchewan Health Authority Clinical Assistant Professor, College of Medicine, University of Saskatchewan, Clinical Assistant Professor, College of Pharmacy, University of Saskatchewan; Regina	Saskatchewan	Advisory Board Member: BMS Pfizer Speaker Honorarium: BMS, Pfizer, Astra Zeneca, Sanofi, Servier, Bayer, BI
Tuchak, Carmen	MD FRCPC Physical Medicine and Rehabilitation Associate Clinical Professor, University of Alberta, Division of Physical Medicine and Rehabilitation, University of Alberta, Edmonton	Alberta	No conflicts to declare
Tebbutt, Tammy	RN, MN District Stroke Coordinator Waterloo Wellington, Kitchener	Ontario	No conflicts to declare
Udell, Jacob	MD, MPH, FRCPC, Scientist, Women's College Research Institute Cardiologist, Women's College Hospital; Assistant Professor, Division of Cardiology, Department of Medicine, Faculty of Medicine, University of Toronto; Affiliate Scientist, Li Ka Shing Knowledge Institute, St. Michael's Hospital; Adjunct Scientist, Cardiovascular & Diagnostic Imaging, Institute for Clinical Evaluative Sciences, Toronto * Appointed as rep by Canadian Cardiovascular Society	Ontario	Advisory board member: .Boehringer-Ingelheim, Novartis, Sanofi Secondary analysis of banked biospecimens from a completed RCT: Janssen Consultant on clinical research development, no involvement in marketing: AstraZeneca, Boehringer Ingelheim, Janssen, Sanofi. Grant to UHN for clinical trial (AstraZeneca); grant to UHN for clinical trial and honorarium for leadership of a multicenter RCT (Boehringer-Ingelheim); grant to WCH for clinical research study (Janssen); grant to WCH to be a site in a multicenter RCT and honorarium for steering committee membership in cohort study (Novartis); grant to WCH for site participation in a multicenter RCT and honorarium for national co-PI role in multicenter RCT (Sanofi) Grants to my institutions for clinical trial participation: Boehringer-Ingelheim; Novartis; Sanofi
van Gaal, Stephen	MD FRCPC Clinical Assistant Professor, University of British	British Columbia	Physician at enrolling site: Portola, Bayer

	Columbia, Vancouver		
Villaluna, Karina	BSN, RN, CCRP, CNN(c) Clinical Research Coordinator and Program Manager Vancouver Stroke Program, Vancouver	British Columbia	Clinical Research Coordinator through the Vancouver Stroke Program Research Office: NoNO Inc, Portola and BMS

APPENDIX TWO:

Canadian Stroke Best Practice Recommendations

Secondary Prevention of Stroke External Reviewers 2020

External Reviewer	Professional Role	Location	Declared Conflicts of Interest
Andrade, Jason	MD, FRCPC Cardiologist, Vancouver General Hospital Associate Professor, University of British Columbia Assistant Professor, Universite de Montreal	Quebec	**Honorarium:** Medtronic, BMS/Pfizer, Bayer, Servier Clinical Studies: Medtronic, Baylis -
Bhatia, Rohit	MD, DM, DNB Professor, Department of Neurology Neurosciences Centre, All India Institute Of Medical Sciences, New Delhi	India	No conflicts to declare
Burns, Margie	PhD, RN Assistant Professor, Faculty of Nursing University of Prince Edward Island	Prince Edward Island	No conflicts to declare
Cora, Elena Adela	MD, PhD, FRCR Assistant Professor, Dalhousie University Interventional and Diagnostic Neuroradiologist	Nova Scotia	No conflicts to declare
Cournoyer, Roxanne	RN Infirmière clinicienne au suivi systématique Clientèle de neurologie vasculaire, CHUM	Quebec	No conflicts to declare
Derex, Laurent	MD Stroke Centre, Department of Neurology, Neurological Hospital Hospices civils de Lyon, University of Lyon, France	Lyon, France	Member of an advisory board: Servier Honorarium: Pfizer -
Dorian, Paul	MD, MSC Professor of Medicine, University of Toronto Staff Cardiologist, St. Michael's Hospital	Ontario	Board member**:** Bayer Inc, BMS, Pfizer, Servier Honorarium for educational activities**:** Bayer Inc, BMS, Pfizer, Servier

			Research participant : Bayer Inc, BMS, Pfizer, Servier
Duffy, Charles	MD, CCFP(EM), FCFP Medical Director, Island EMS; Emergency Physician, Queen Elizabeth Hospital	Prince Edward Island	No conflicts to declare
Ehrensperger, Eric	MD, MSc, FRCPC Assistant Professor McGill University; Stroke Neurologist, McGill University Health Centre	Quebec	No conflicts to declare
Flomin, Yuriy	MD, PhD Head, Acute Stroke and Neurorehabilitation Unit, Medical Center 'Universal Clinic 'Oberig'; Board Member, NGO 'Ukrainian Anti-Stroke Association'; Associate Professor, Department of Neurology, Bogomolets National Medical University, Kyiv, Ukraine	Ukraine	Advisory Board, Honorarium, Other payment or In-Kind: Boehringer Ingelheim, Pfizer, Bayer, Sanofi, Takeda
George-Phillips, Kirsten	Clinical Practice Leader, Alberta Health Services	Alberta	Speaker Bureau: Pharmacists Association of Alberta
Grant, Sarah	RN, BSCN Stroke Nurse Clinician, Stroke Rapid Assessment Unit, Nanaimo General Hospital	British Columbia	No conflicts to declare
Gupta, Milan	MD, FRCPC, FCCS Associate Clinical Professor of Medicine, McMaster University; Medical Director, Canadian Collaborative Research Network, Brampton	Ontario	Advisory board, lectures: AstraZeneca, Amgen, Sanofi, Novartis, HLS -
Jain, Rahul	MD, CCFP, MScCH(HTPE) Assistant Professor, Department of Family and Community Medicine, University of Toronto	Ontario	No conflicts to declare
Jalini, Shirin	MD, FRCPC Assistant Professor, Division of Neurology, Queen's University, Kingston	Ontario	No conflicts to declare
Jickling, Glen	Neurologist, University of Alberta, Edmonton	Alberta	Research Grant: Heart and Stroke Foundation, CIHR, University Hospital Foundation.

Kamel, Hooman	MD, MS Vice Chair for Research, Department of Neurology Weill Cornell Medicine Chief, Division of Neurocritical Care; Director, Clinical and Translational Neuroscience Unit; Department of Neurology | Feil Family Brain and Mind Research Institute; Weill Cornell Medicine	New York, USA	Endpoint adjudication committee**:** Boehringer-Ingelheim Editor**:** JAMA Neurology Co-PI**:** ARCADIA trial, ASPIRE trial Support for ARCADIA trial: BMS-Pfizer, Roche Steering committee: Stroke-AF trial -
Kao, Hong	BSc, Pharm Clinical Pharmacist Comprehensive Stroke Unit, Trillium Health Partners	Ontario	No conflicts to declare
Keon, Lisa	RN, BsCN Nurse Specialist Stroke Prevention Clinic Pembroke Regional Hospital	Ontario	No conflicts to declare
Korec, Lisa	RN, BN, CON(C) Director of Neurosciences, Provincial – Saskatchewan Health Authority	Saskatchewan	Advisory Board: Heart and Stroke Foundation
Legault, Catherine	Assistant Professor - Department of Neurology &Neurosurgery McGill University; at the Montreal Neurological Institute	Quebec	Heart and Stroke Foundation Board Member.
Macdonald, Gerald	MN RN, CCN(C) Cardiac Rehabilitation Nurse (Grande Prairie) North Zone Chronic Disease Management Alberta Health Services	Alberta	I may have holdings in a drug company, only as a part of my Group RRSP in a mutual fund portfolio Member of Canadian Council of Cardiovascular Nurses
Mancini, GB John	MD, FRCPC, FACC Professor of Medicine, Division of Cardiology University of British Columbia	British Columbia	Advisory Board, CME lectures, Research Grants; Member of speaker's bureau; Received payment from an organization: HLS Therapeutics, Astra Zeneca, Amgen, Sanofi, Novonordisk, Esperion, Boeringher Ingelheim/Lilly, Janssen Investigator**:** NIH, Novonordisk, Amgen -

Murphy, Kaylee	MD, CCFP	Prince Edward Island	No conflicts to declare
Ng, Kelvin Kuan Huei	M.B.B.S. Associate Professor in Medicine, McMaster University Stroke and General Internal Medicine Specialist	Ontario	No conflicts to declare
Peacock, Darlene	RN Stroke Navigator for Grande Prairie, AB Stroke Prevention Clinic	Alberta	No conflicts to declare
Roussin, Andre	Associate Professor of Medicine, Department of Medicine, CHUM, University of Montreal	Quebec	Advisory boards**:** Bayer, BMS, Pfizer, Sanofi, Servier Co-investigator: VOYAGER-PAD, BRAIN-AF
Schaafsma, Joanna Danielle	MD, MSc(Hon) Vascular Neurologist, Stroke Program and Vascular Malformation Clinic, Division of Neurology, Department of Medicine, University Health Network, University of Toronto	Ontario	Received grant: Non for profit Ministry of Health and Longterm Care, Ontario Medical Association Site PI: phase III trial
Senior, Peter	MBBS, PhD Professor of Medicine, Division of Endocrinology and Metabolism University of Alberta, Edmonton, AB	Alberta	Consulting / advisory boards (none since 2018): Novo, Lilly, Sanofi, Astra Zeneca, Jannsen, Boehringer Ingelheim, Abbott Previously delivered accredited CME programs to family physicians re treatments for diabetes and its complications (none since 2018): Novo, Lilly, Sanofi, Astra Zeneca, Jannsen, Boehringer Ingelheim, Abbott Honorarium for CPG chair role: Diabetes Canada. JDRF Local PI for clinical trial of GLP1 in diabetic eye disease and kidney disease: Novo Nordisk. Local Co-I in clinical trial of stem cell derived beta cell product for type 1 diabetes: Viacyte Chair Diabetes Canada Clinical Practice Guidelines Steering Committee - convergence of interest

Tkach, Aleksander	MD Medical Director Stroke and EVT Interior Health BC	British Columbia	Speaking honorarium 250CAD:University of Utah - Numerous clinical multisite trials for over 10 years - I have never been paid by any of these trials as a site PI
Williams, Janice	RN(EC) NP-Adult, CCN(c) Nurse Practitioner, Stroke Program UHN-TWH Adjunct Lecturer, Faculty of Nursing, University of Toronto	Ontario	No conflicts to declare

Appendix Three: Pharmacotherapy for Smoking Cessation in Patients with Stroke and TIA

This table provides a summary of the pharmacotherapeutic properties, side effects, drug interactions and other important information on the current medications available for use in Canada. This table should be used as a reference guide by health care professionals when selecting an appropriate agent for individual patients. Patient compliance, patient preference and/or past experience, side effects, and drug interactions should all be taken into consideration during decision-making, in addition to other information provided in this table and available elsewhere regarding these medications.

Note: NRT – nicotine replacement therapy

	Nicotine patch	Nicotine gum	Nicotine inhaler	Nicotine Lozenge	Bupropion	Varenicline
Initial Treatment Length	8-12 weeks	4-36 weeks	12-24 weeks	4-24 weeks	7-12 weeks	12 -24 weeks
Time to Peak Effect	Requires 2-3 days to get maximal serum levels	After 20-30 min of chewing	Within 15 minutes after forced inhalation for 20 minutes	After 20-30 min of sucking	1-2 weeks	1-2 weeks
Indications	As an aid to smoking cessation				As an aid to smoking cessation, major depressive disorder, seasonal affective disorder	As an aid to smoking cessation
Usual Dosing	Starting dose can be adjusted based on cig/d 24 Hour patch: 21 mg for 3 to 6 weeks, then 14 mg for 2 to 4 weeks then 7 mg for 2 to 4 weeks. 16 Hour patch: 15mg for 6 weeks then10mg for 2 weeks then 5mg for 2 weeks	<25 cig/d or smokes >30 min upon waking: 2 mg >25 cig/d or smokes <30 min upon waking: 4 mg Week 1-6; 1 piece q1-2h (at least 9/d) Week 7-9: 1 piece q2-4h Week 10-12: 1 piece q4-8h Can use prn when concurrent patch Stop when reduced to 1-2 per day Max: 20-30 pieces per day	Weeks 1-12: 6-12 cartridges per day then gradually reduce as able. (min 6/d for first 3-6 weeks) Stop when reduced to 1-2 per day Max: 12 cartridges per day	Polacrilex: Smokes >30 min upon waking: 2mg Smokes <30 min upon waking: 4mg Bitartarate: < 20 cig/d: 1 mg > 20 cig/d: 2 mg Week 1-6; 1 lozenge q1-2h Week 7-9: 1 piece q2-4h Week 10-12: 1 piece q4-8h Stop when reduced to 1-2 per day	150 mg once daily x 3 days then 150 mg BID x 7-12 weeks. Begin 1-2 weeks prior to selected quit date If successful in quitting, an ongoing maintenance therapy may be considered	0.5 mg once daily x 3 days then 0.5 mg BID x 4 days then 1 mg BID x 11 weeks. Begin 1-2 weeks prior to selected quit date. If successful in quitting, an additional 12-week course may increase likelihood of success

	Nicotine patch	Nicotine gum	Nicotine inhaler	Nicotine Lozenge	Bupropion	Varenicline
				Max: 30 mg/day		
Dosage adjustment in organ dysfunction	Nicotine clearance is decreased in moderate to severe renal impairment; consider dose reduction Nicotine clearance is decreased in moderate to severe hepatic impairment; consider dose reduction				Use with caution in renal impairment and hepatic impairment: Specific dosing recommendations not provided	CrCl < 30mL/min: Max 0.5mg BID ESRD (receiving hemodialysis): Max 0.5mg daily
Special Dosing Notes	Smokers are precise in the way they titrate their smoking to maintain nicotine levels, and dosing should be titrated and personalized accordingly. A common issue is under dosing NRT in heavier smokers. Dosing guide: 1 cigarette = 1 mg nicotine. E.g., if smoke 2 packs per day, offer 2 x 21mg patches plus gum or inhaler for cravings. In the "Reduce to Quit" approach, patients may continue to smoke while on the patch as they are receiving nicotine via the patch/gum/lozenge/inhaler and should be smoking fewer cigarettes, which is the goal.				Must titrate dose when discontinuing Take second daily dose early to minimize insomnia	Upward titration to reduce nausea from drug
Side Effects	Headache, GI upset, dizziness, nausea, disturbed sleep, rash at site	Headache, GI upset, hiccups, disturbed sleep, sore jaw	Irritation of throat and nasal passages, sneezing, coughing especially in those with bronchospastic disease, hiccups	GI upset, mouth/throat soreness, hiccups	Dry mouth, insomnia, agitation, vivid dreams, unease. Risk of seizure is 1/1000 (risk factors include those with seizure or eating disorders)	Nausea, insomnia, abnormal/vivid dreams. Health Canada warning for psychiatric effects
Effect of Food and Other Administration Notes	Do not cut patch, causes rapid evaporation rendering product useless. Rotate patch site to avoid skin irritation.	Recent food and beverage impair release of nicotine. Avoid food and drink 15 min before or while using gum (30 min for caffeine/acidic products). Not regular chewing gum; use bite, chew, park technique.	Not a true inhaler (is a vaporizer) so best effect with continuous puffing; nicotine absorbed from oral mucosa. Cold temperatures can decrease absorption rate.	Recent food and beverage impair release of nicotine. Avoid food and drink 15 min before or while using lozenge.	Sustained release product; do not crush or chew.	No food cautions.
Drug Interactions	Nicotine itself is not subject to cytochrome P-450 interactions. Tobacco smoke however leads to potent induction of CYP1A1 and 1A2. When smoking is discontinued, the substrate drug may require a dosage decrease over a period of several days. CYP1A1, 1A2 substrates include: theophylline, clozapine, olanzapine, fluvoxamine, TCAs (partial substrate).				Inhibits CYP2D6, 2B6 substrate, avoid with MAOI	Increased levels/effects of NRT

	Nicotine patch	Nicotine gum	Nicotine inhaler	Nicotine Lozenge	Bupropion	Varenicline
Contraindications/ Cautions	Life-threatening arrhythmias, severe angina, atopic/eczematous dermatitis or other skin conditions (e.g., psoriasis)	Life-threatening arrhythmias, severe angina, dental problems, temporomandibular joint syndrome	Life-threatening arrhythmias, severe angina	Life-threatening arrhythmias, severe angina	Seizure disorder, anorexia, bulimia, use of MAOI in 14 days, patients undergoing abrupt discontinuation of alcohol, sedatives and benzodiazepines	Depression, suicidal ideation, schizophrenia, bipolar, major depressive disorders *See Note below
Use in Special Populations	• Cardiovascular/Stroke Patients: Demonstrated safety in stable cardiovascular disease (possible exceptions are unstable angina, recent MI, unstable arrhythmia, acute heart failure). Commonly used in many inpatient settings as symptoms of nicotine withdrawal can begin within 1 hour. It is considered by many experts as far safer than continued smoking. • Pregnancy/Breastfeeding/Adolescents: While data are limited in pediatrics and pregnant/breastfeeding women, NRT is generally considered safer than smoking in these populations and should be considered. Offer the lowest effective dose of a short-acting nicotine product to minimize nicotine exposure.				May be used in pregnant women, especially those with depression. May be considered in adolescents or breastfeeding women.	Data not available in pregnancy/lactation. May be considered in adolescents.
Combination Therapy?	Can use with oral agents, gum, inhaler or lozenges. Evidence suggests better abstinence rates with combination over monotherapy.	Can use with oral agents or patch. Evidence suggests better abstinence rates with combination over monotherapy.			Can use with varenicline or NRT. Addition of patch significantly increases long term cessation compared with patch alone. Monitor for treatment emergent hypertension when NRT is combined with bupropion.	Can use with bupropion or NRT (although increased adverse effects with NRT).
Mechanism of Action	Partially replaces nicotine delivered by cigarettes				Not fully understood. Likely due to inhibition of dopamine and norepinephrine uptake.	Partial agonist at nicotinic acetylcholine receptor, causing decreased dopamine release and activation of mesolimbic reward system.
Approximate $ per month	$100	$75-200 (6-20 pieces/d)	$175- 350 (6-12 cartridges/d)	$100-250 (6-12 lozenges/d)	$60	$60

***Note:** on September 14, 2016, a joint meeting of the U.S. Food and Drug Administration's (FDA) Psychopharmacologic Drugs Advisory Committee and Drug Safety Risk Management Advisory Committee reviewed data from EAGLES (Evaluating Adverse Events in a Global Smoking Cessation Study) evaluating the neuropsychiatric safety of Champix® (varenicline) to determine whether the findings support changes to the product labeling in the US. By a majority vote, the Advisory Committee recommended to remove the boxed warning regarding serious neuropsychiatric adverse events from the labeling. At the time of publication of these recommendations, Canadian product monographs have not changed.*

Appendix Four: Oral Anticoagulants for the Prevention of Stroke in Atrial Fibrillation Patients

This table provides a summary of the pharmacotherapeutic properties, side effects, drug interactions and other important information on the five anticoagulant medications currently in use in Canada for the prevention of stroke and systemic embolism in atrial fibrillation. This table should be used as a reference guide by health care professionals when selecting an appropriate agent for individual patients. Patient compliance, side effects, drug interactions and bleeding risk status should all be taken into consideration during decision-making, in addition to other information provided in this table and available elsewhere regarding these medications.

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban	Warfarin
Mechanism of Action	Direct Xa inhibitor	Direct thrombin inhibitor	Direct Xa inhibitor	Direct Xa inhibitor	Vitamin K antagonism of factors II, VII, IX, X
Stroke Indications	Prevention of stroke and systemic embolism in non-valvular atrial fibrillation Prevention of VTE in THR or TKA Treatment of venous thromboembolic events (DVT and PE).	Prevention of stroke and systemic embolism in non-valvular atrial fibrillation Prevention of VTE in THR or TKR Treatment of venous thromboembolism events (e.g., DVT, PE) and prevention of recurrent DVT and PE	Prevention of stroke and systemic embolic events in patients with non-valvular atrial fibrillation. Treatment of VTE (DVT and PE) and the prevention of recurrent DVT and PE	Prevention of stroke and systemic embolism in non-valvular atrial fibrillation Prevention of VTE in THR or TKR Treatment of venous thromboembolic events (e.g., DVT, PE) and prevention of recurrent DVT and PE In combination with ASA (75-100mg) for the prevention of stroke, myocardial infarction and cardiovascular death and for the prevention of acute limb ischemia and mortality in patients with coronary artery disease with or without peripheral artery disease	Prophylaxis and/or treatment of VTE, atrial fibrillation with embolization, and as an adjunct in the prophylaxis of systemic embolism after myocardial infarction, including stroke and reinfarction

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban	Warfarin
Active bleeding or significant risk factors for bleeding	Active bleeding or significant risk factors for bleeding Concurrent therapy with Strong CYP 3A4& P-gp inhibitors (e.g., azoles, ritonavir) Moderate to severe hepatic impairment associated with coagulopathy and clinically relevant bleeding risk Pregnant/Breastfeeding Concomitant treatment with other anticoagulants	Active bleeding or significant risk factors for bleeding **CrCl<30 ml/min** Concurrent therapy with Strong P-gp inducer (e.g., rifampin) Pregnant/Breastfeeding	Clinically significant active bleeding including GI bleeding. Lesions or conditions at increased risk of clinically significant bleeding, Hepatic disease associated with coagulopathy and clinically relevant bleeding risk. Pregnancy/Breastfeeding Concomitant treatment with other anticoagulants.	Active bleeding or significant risk factors for bleeding Concurrent therapy with Strong CYP3A4 & P-gp inhibitors (e.g., azoles, ritonavir) Pregnancy/Breastfeeding Moderate to severe hepatic impairment associated with coagulopathy and clinically relevant bleeding risk	Active bleeding or significant risk factors for bleeding Pregnancy
Side Effects	Bleeding: Lower risk of bleeding vs. warfarin	Gastritis-like symptoms; dyspepsia, Bleeding: 150 mg BID – similar bleeding risk to warfarin; but higher risk of GI bleed 110 mg BID – lower bleeding risk than warfarin;	Bleeding: Lower risk of bleeding vs warfarin.	Bleeding: Similar risk to warfarin overall. Higher risk of transfusion vs. warfarin. Higher risk of GI bleed vs. warfarin.	Bleeding: Purple toe syndrome (rare)
Landmark Trials	ARISTOTLE NEJM 2011;365:981-92 AVERROES NEJM 2011; 364:806-817.	RE-LY NEJM 2009;361:1139-51	ENGAGE AF-TIMI 48 N Engl J Med; 2013;369:2093-2104	ROCKET-AF NEJM 2011;365:883-91	Multiple RCTs and Meta-Analyses in both valvular and non-valvular Atrial Fibrillation
Inclusion Criteria	Documented AFib or AFlutter plus at least one of: Previous stroke, TIA, systemic embolism Age >75 Heart failure DM HTN requiring treatment	Documented non-valvular Fib within 6 mos and at least 1 of: Previous stroke/TIA Heart failure Age > 75 Age >65 + DM HTN CAD	Documented AFib with a CHADS2 score of 2 or higher and anticoagulation therapy planned for the duration of the trial	Documented non-valvularAFib, with history of stroke, TIA, or systemic embolism or at least 2 of the following: Heart failure HTN Age >75 DM	

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban	Warfarin
Exclusion Criteria	AFib due to reversible cause Moderate or severe valvular disease Stroke in past 7 days CrCl<25 ml/min Need for ASA+clopidogrel or ASA >165 mg/d	Severe heart-valve disorder Stroke within 14 days Severe stroke within 6 months Condition that increased risk of hemorrhage CrCl<30ml/min Active liver disease Pregnancy ASA >100 mg/d	AFib due to a reversible disorder; an estimated creatinine clearance of < 30 mL/min; a high risk of bleeding; use of dual antiplatelet therapy; moderate to severe mitral stenosis; other indications for anticoagulation therapy; acute coronary syndromes, coronary revascularization or stroke within 30 days prior to randomization; and an inability to adhere to study procedures.	Severe heart valve disease TIA caused by reversible disorder Active IE Conditions that increase risk of hemorrhage Uncontrolled HTN Stroke within 14 days or severe stroke within 3 months Significant liver disease Use of strong CYP 3A4 inhibitors Chronic NSAIDs Pregnancy HIV CrCl<15ml/min ASA >100mg/d	
Primary Outcome Measures: Stroke and Systemic Embolism Event Rate	Stroke/systemic embolism: 1.27%/yr Stroke: 1.19%/yr Warfarin: 1.51%yr	Stroke/systemic embolism: 110mg: 1.53% 150mg: 1.11% Warfarin: 1.69%/yr Stroke: 110mg: 1.44%/yr 150mg: 1.01%/yr Warfarin: 1.57%/yr	Edoxaban 60 mg day vs warfarin Stroke/systemic embolism: 1.18/yr vs 1.5%/yr	Stroke/systemic embolism: 1.7%/yr Warfarin: 2.2%/yr Stroke: Not a primary outcome	Stroke/systemic embolism: ARISTOTLE: 1.60%/yr RE-LY: 1.69%/yr ENGAGE: 1.50%/yr ROCKET-AF: 2.2%/yr Stroke: ARISTOTLE: 1.51%yr RE-LY: 1.57%/yr ENGAGE: 1.69%/yr ROCKET-AF: not measured
Overall Bleeding	18.1%/yr	110 mg: 14.6%/yr 150 mg: 16.4%/yr	14.5%/yr	14.9 per 100 pt-yr	RE-LY: 18.2%/yr ROCKET-AF: 14.5 per 100 pt-yr ARISTOTLE: 25.8%yr ENGAGE: 16.40%/yr

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban	Warfarin
Major Bleeding	2.13%/yr	110 mg: 2.7%/yr 150 mg: 3.1%/yr	2.75%/yr	3.6 per 100 pt-yr	RE-LY: 3.4%/yr ROCKET-AF: 3.4 per 100 pt-yr ARISTOTLE: 3.09%/yr ENGAGE: 3.43%/yr
ICH	0.33%/yr	110 mg: 0.23%/yr 150 mg: 0.30%/yr	0.39%/yr	0.5 per 100 pt-yr	RE-LY: 0.74%/yr ROCKET-AF: 0.7 per 100 pt-yr ARISTOTLE: 0.8%/yr ENGAGE: 0.85%/yr
GI Bleed	0.76%/yr	110 mg: 1.1%/yr 150 mg: 1.5%/yr	1.51%/yr	3.2% (over 1.86 yrs on drug)	RE-LY: 1%/yr ROCKET-AF: 2.2% ARISTOTLE: 0.86%/yr ENGAGE: 1.23%/yr
Drug Interactions **** Note: This is NOT a complete list, rather examples of some of the more frequent or serious drug interactions with these OACs.***	CYP3A4 and P-glycoprotein (e.g., anticonvulsants, rifampin, dexamethasone, trazodone, amiodarone, cyclosporine, diltiazem, verapamil, azole antifungals, macrolides, efavirenz, ritonavir, St. John's Wort) Other agents that effect bleeding	P-glycoprotein (e.g., carbamazepine, rifampin, dexamethasone, trazodone, amiodarone, dronedarone, quinidine, cyclosporine, diltiazem, verapamil, ketoconazole, St. John's Wort) Acid neutralizers Other agents that effect bleeding	Concomitant strong inhibitors/inducer of P-gp will impact edoxaban exposure. Anticonvulsants, rifampin, amiodarone, dronedarone, azole antifungals, macrolides, quinidine, verapamil, St. John's Wort, other agents that effect bleeding	CYP3A4 and P-glycoprotein (e.g., anticonvulsants, rifampin, dexamethasone, trazodone, amiodarone, cyclosporine, diltiazem, verapamil, azole antifungals, macrolides, efavirenz, ritonavir, St. John's Wort) Other agents that effect bleeding	CYP2C9 and CYP3A4 (e.g., anticonvulsants, rifampin, amiodarone, azole antifungals, macrolides, efavirenz, St. John's Wort), vitamin K containing foods, other agents that effect bleeding
Comments		Prodrug – dabigatran exetilate (needs acidic environment for optimal absorption)			
Time to Peak Effect	1-3 hours	1-3 hours	1-2 h	3-4 hours	3-5 days
Half-life	8-15 hours	14-17 hours	10-14h	7-11 hours	20-60 hours
Bioavailability	66%	6%	62%	>80%	Rapid and extensive

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban	Warfarin
Renal Excretion of unchanged Active Drug	27% renal	80% renal	50%	36% renal	Minimal
Effect of Food	No reported effect	Delayed absorption	Food increases peak exposure to varying degrees, but has minimal effect on total exposure – take with or without food	Increases absorption of 20 mg dose but not 10 mg dose (take with food)	Slows rate but not extent; Vitamin K content should be kept consistent
Usual Dosing in Atrial Fibrillation	5mg BID 2.5mg BID if ≥2 of: age≥80, wt≤60kg, SrCr≥133	150mg BID 110mg BID	60 mg once daily 30 mg once daily if any one of the following: weight ≤ 60kg; or if CrCl between 30-50 mL/min	20mg OD 15mg OD (if CrCl 30-49)	Initial: 2.5-10 mg daily Maintenance based on INR (target 2.5, range 2-3)
Consideration in Renal Dysfunction	Determine estimated creatinine clearance in all patients before initiating using Cockroft-Gualt formula. For prevention of stroke and systemic embolism in patients according to renal function. Reduction in dose to 2.5 mg bid, if 2 or more of the following criteria are met: - Age > 80 years - Body weight < 60 kg - Serum creatinine > 133 mcmol/L In patients with CrCl >25 ml/min In patients >15, <24 mL/min – no dosing recommendation due to very limited clinical data <15mL/min or undergoing dialyisis – not recommended	Determine estimated creatinine clearance in all patients before initiating using Cockroft-Gualt formula. For prevention of stroke and systemic embolism in patients according to renal function: No dose adjustment is generally needed in patients with moderate renal impairment (CrCl 30-50mL/min)	Determine estimated creatinine clearance in all patients before initiating using Cockroft-Gualt formula. CrCl 30-50 mL/min 30 mg daily CrCl < 30mL/min – not recommended	Determine estimated creatinine clearance in all patients before initiating using Cockroft-Gualt formula. Indicated in patients with CrCl as low as 15 mL/min: For prevention of stroke and systemic embolism in patients with atrial fibrillation decrease dose to 15mg daily in patients with moderate to severe renal dysfunction (49-15 mL/min) Not indicated in those patients with CrCl <15 mL/min	

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban	Warfarin
Anticoagulation Monitoring	Not Required	Not Required	Not required	Not Required	Regular INR testing
Additional Monitoring	SCr at baseline and at least annually	SCr at baseline and at least annually	SCr at baseline and at least annually	SCr at baseline and at least annually	
Antidote /Reversal ***The shorter half-lives of the four DOACs and their impact on only one aspect of the clotting cascade relative to warfarin will allow for more rapid elimination in the context of normal renal function**	Antidote*: not yet available in Canada; studies with Andexanet ongoing. Octaplex/Beriplex (Prothrombin Complex) - may be considered for use in major bleeding (Off-label use and supplied by Canadian Blood Services) Prothrombin complex concentrate may provide benefit though not supported by clinical trials Some suggestion that activated charcoal if ≤2hr (potentially out to 6 hours) based on one small trial.	Antidote*: Praxbind® (idarucizumab) Some suggestion that activated charcoal if ≤2hr or dialysis (though not likely feasible if patient hypotensive and/or experiencing marked blood loss) may provide benefit though not supported by clinical trials Administer 2 - 2.5 g doses by IV infusion (5-10 mins for each vial) within 15 minutes of each other or as consecutive IV boluses	Antidote*: not yet available in Canada; studies with Andexanet Octaplex/Beriplex (Prothrombin Complex) - may be considered for use in major bleeding (Off-label use and supplied by Canadian Blood Services) Some suggestion that activated charcoal if ≤3hr or prothrombin complex concentrate may provide benefit though not supported by clinical trials	Antidote*: not yet available in Canada; studies with Andexanet Octaplex/Beriplex (Prothrombin Complex) - may be considered for use in major bleeding (Off-label use and supplied by Canadian Blood Services) Prothrombin complex concentrate may provide benefit though not supported by clinical trials - Prothrombin Complex Concentrate has very preliminary evidence in 12 healthy volunteers (Circulation 2011;124:1573–1579 [limited study]) Some suggestion that activated charcoal if ≤2hr (potentially out to 8 hours) based on one small trial.	Vitamin K and Prothrombin Complex Concentrate: (*Chest* 2012;141;e152S-e184S)
Hold for Invasive Surgery	At least 24 hours Resumed postoperatively when homeostasis ensured	1-2 days (if CrCl≥50) 3-5 days (if CrCl<50) Hold for 24 hours prior to ablation for atrial fibrillation Resumed postoperatively when homeostasis ensured	At least 24 hours Resumed postoperatively when homeostasis ensured	At least 24 hours Resumed postoperatively when homeostasis ensured	5 days Resumed postoperatively when homeostasis ensured

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban	Warfarin
$ per month/coverage in Canada	Special authorization for AFib in public drug plans $3.20/day	Special authorization for AFib in public drug plans $3.20/day	Special authorization for AFib in public drug plans $2.84/day	Special authorization for AFib in public drug plans $2.84/day	Full benefit $0.06/day, $1.16/day including monitoring costs
Switching from warfarin to DOAC	Start after warfarin discontinued and INR<2.0	Start after warfarin is discontinued and INR<2.0	Start after warfarin discontinued and INR≤2.5	Start after warfarin discontinued and INR≤2.5	
Switching from DOAC to warfarin	Initiate warfarin and continue apixaban until INR≥2.0 Note that PT/INR is impacted by apixaban During concomitant therapy, initiate INR testing on day 3 and just before apixaban dose	CrCl>50ml/min: start warfarin 3 days before discontinuing dabigatran CrCl 31-50ml/min: start warfarin 2 days before discontinuing dabigatran CrCl 15-30ml/min: start warfarin 1 day before discontinuing dabigatran Note that PT/INR may be impacted by dabigatran	Give edoxaban 30 mg daily (15 mg daily of those on a reduced dose) concurrently with warfarin until INR is ≥2.0 then stop edoxaban	CrCl>50ml/min: start warfarin 4 days before planning to discontinue rivaroxaban CrCl 31-50mL/min: start warfarin 3 days before planning to discontinue rivaroxaban CrCl 15-30mL/min: start warfarin 2 days before planning to discontinue rivaroxaban Continue rivaroxaban with warfarin until INR≥2.0. Use usual warfarin start dose for first 2 days of therapy. Note that PT/INR is impacted by rivaroxaban During concomitant therapy, perform INR testing just before rivaroxaban dose (and at least 24 hours after previous rivaroxaban dose)	

Note: * The MDRD equation has not been validated to guide the adjustment of drug doses in renal impairment so use of the Cockcroft-Gault equation is still recommended. While it is likely that in many cases when the eGFR is 60 mL/min or less that the calculated creatinine clearance will be very similar to the eGFR, differences could occur if the person has a body surface area significantly lower or higher than 1.73 m^2, or at different stages of renal disease. Drug dose adjustment is based on the actual GFR and the best way of calculating this remains the Cockcroft-Gault equation. The FDA standard for drug dosing recommendations is the Cockroft-Gault equation. (Sources for Additional Information: http://www.bpac.org.nz/magazine/2007/june/renal.asp?page=3; Moranville and Jennings, Am J Health-Syst Pharm. 2009; 66:154-61)