CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

Secondary Prevention of Stroke

Update 2017 (FINAL)

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Canadian Stroke BestPractice Recommendations
Prevention of Stroke ~ Sixth Edition **(UPDATEOCTOBER 2017)**

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Section One: INTRODUCTION and OVERVIEW

Introduction

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 [unpaid] caregivers). The goal of timely updating, disseminating and implementing these recommendations is to promote and support evidence-based stroke care across Canada, increase capacity for stroke service delivery, reduce practice variations in the care of stroke patients, and drive quality improvement to reduce the gap between current knowledge and clinical practice.

The CSBPR are under the leadership of the Heart and Stroke Foundation, Canada (HSF) and involve over 200 volunteers from across Canada and internationally, including healthcare professionals with stroke expertise and stroke patients and families. The writing group and external reviewers involved in this update of the Secondary Prevention of Stroke recommendations 2017 are listed in Appendix One.

The recommendations are developed and presented within a continuous improvement model. The primary target audience for these recommendations includes all healthcare providers from a range of health disciplines who are involved in the planning, delivery and monitoring of quality stroke care. They are also written for health system planners, funders, administrators, and healthcare professionals, all of whom have important roles in the optimization of stroke prevention and care and who are accountable for results.

Stroke Care in Canada

- Every year, approximately 62,000 people with stroke and transient ischemic attack present to Canadian hospitals for assessment and treatment. Many patients who experience a minor stroke or transient ischemcic attach (TIA) may present to primary care and ambulatory stroke clinics without hospital admission, therefore the total incidence of stroke is even larger. Moreover, it is estimated that for each symptomatic stroke, there are nine covert strokes, many with vascular origin, that result in subtle changes in cognitive function and processes.
- Stroke and other cerebrovascular diseases are the third leading cause of death in Canada.
- Stroke is a leading cause of adult disability, with over 405,000 Canadians living with the effects of stroke (CPSR, 2015).
- Stroke patients spendapproximately 639,000 days in acute care hospitals annually (QSCiC, 2012), and account for some of the longest lengths of stay and highest costs.
- The annual cost of stroke is approximately $3.6 billion, taking into account both healthcare costs and lost economic output (Krueger, 2012).
- The human cost of stroke is immeasurable.

The HSF works closely with national and provincial stakeholders and partners to develop and implement a coordinated and integrated approach to stroke prevention, treatment, rehabilitation, and community reintegration in every province and territory in Canada. The CSBPR provides a common set of guiding principles for stroke care delivery, and describes the infrastructure necessary at a system level, and the clinical protocols and processes that are needed to achieve and enhance integrated, high-quality, and efficient stroke services for all Canadians. Through the innovations embodied within the stroke best practices, these guidelines contribute to health system reform in Canada and internationally.

The theme of the Sixth Edition of the CSBPR is *Partnerships and Collaborations*. This theme stresses the importance of integration and coordination across the healthcare system to ensure timely and seamless care of stroke patients to optimize recovery and outcomes. Involvement of individuals who have had a stroke, their families and caregivers, is paramount to collaborations and partnerships and emphasized a patient and family-centred approach to stroke care delivery. Working with interprofessional stroke care team members, other vascular care groups, emergency medical services, community care providers, educators, researchers, health system funders, planners and managers, will strengthen our ability to reduce risk factor prevalence, incidence, morbidity, and mortality from stroke.Individuals who experience a stroke present with additional health conditions or issues simultaneously, which increases the challenges and complexity of comprehensive stroke management. Partnerships and collaborations withother healthcare providers from a range of specialties is imperative to ensure people withmultimorbiditieshave optimal control of each condition, do not fall through the cracks, do not receive conflicting or contra-indicated treatments, and receive support to navigate the various areas of the healthcare system. Partnerships and collaborations are also necessary to support stroke care in rural and remote settings where some basic stroke services may not be available and people experiencing a stroke in those regions may not have access to optimal treatment strategies, which may result in poorer outcomes.

This theme aligns with and supports the *HSF Promote Recovery* mission priority and is included as part of each module for the 2016-2018 update of the *Canadian Stroke Best Practice Recommendations.*

Partnerships and Collaborations to achieve optimal outcomes is an imperative within secondary stroke prevention and applies across the system of care, with the participation of individuals with stroke, their families and caregivers, healthcare providers, and the broader community. A challenge in secondary stroke prevention is the range of settings where stroke prevention services may occur – such as within an emergency department, outpatient/ambulatory care setting, primary care practice, community care services, acute inpatient care and/or within stroke rehabilitation services. Stroke prevention is an ongoing process that occurs over time and involves a range of healthcare expertise; therefore strong and transparent collaborations and partnerships will ensure smooth continuity of care and reduce the risk of complications and recurrent stroke. The primary underpinnings of ‘prevention’ requiresindividuals with stroke and a wide range of healthcare team members to work together to identify risk factors and stroke etiology, agree on goals for prevention of recurrent stroke, and implement appropriate management strategies.

Achieving optimal outcomes for stroke survivors requires rapid access to specialized stroke prevention services; promotion of and support for healthy lifestyles to minimize vascular risk; aggressive risk factor management, especially for blood pressure; appropriate prescription of medications for prevention; compliance with medication regimes and lifestyle changes such as diet, physical activity and smoking cessation; timely access to interventions such as carotid revascularization; and, screening of appropriate patients for smoking status, mood, cognition and obstructive sleep apnea.

For more information, refer to the Canadian Stroke Best Practices Overview and Methodology Manual at www.strokebestpractices.ca.

Secondary Prevention of Stroke Update 2017 Module Overview

Scope of the Secondary Prevention of Stroke Module:

This Secondary Prevention of Stroke module focuses on management 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 TIA 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 Preventitive Health Care, and Canadian Physical Activity Guidelines).

Prevention Definitions:

Primary prevention is 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 is often implemented in the primary care setting, and the physician, advanced practice nurse, pharmacist or patient may initiate a discussion of stroke risk reduction. Primary prevention and health promotion recommendations related to stroke (lifestyle and risk factor management, hypertension screening, dyslipidemia screening, diabetes management, management of atrial fibrillation, and asymptomatic carotid stenosis) emphasize the importance of screening and monitoring those patients at high risk of a first stroke event. Primary prevention strategies to improve population health are led by health-oriented organizations and agencies such as the Heart and Stroke Foundation, Canadian Cardiovascular Society, Hypertension Canada, Diabetes Canada, and Health Canada. The HSF has been actively promoting stroke prevention through their many programs and advocacy campaigns. Primary prevention strategies focusing on children and youth aim to reduce risk profiles of young Canadians, enabling kids to have a healthy development. The strategy focuses on physical activity, tobacco control and healthy eating through the creation of supportive environments where the healthy choice is the easy choice in the home, at schools and other public places where children frequent. Areas of focus include nutrition with an aim to raise the profile of and advocate for policies to restrict food and beverage marketing to children and reduce sugary drink consumptions. These strategies will create healthier populations with a reduced risk of stroke.

Secondary prevention is an individually based clinical approach aimed at reducing the risk of a recurrent vascular events in individuals who have already experienced a stroke or transient ischemic attack and in those who have one or more of the medical conditions or risk factors that place them at high risk of stroke. Secondary prevention recommendations in this document are directed to those risk factors most relevant to stroke, including lifestyle (diet, sodium intake, exercise, weight, smoking, and alcohol intake), hypertension, dyslipidemia, previous stroke or transient ischemic attack, atrial fibrillation and stroke, and carotid stenosis. Secondary prevention recommendations can be addressed in a variety of settings—acute care, stroke prevention clinics, 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 because of stroke or transient ischemic attack.

Recommendations for secondary prevention of stroke 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 a stroke or transient ischemic attack.The health care and stroke system should be set up to ensure secondary prevention is offered and maintained in all stages of stroke care.

Definition of TIA*:*A brief episode of neurological dysfunction caused by focal brain, spinal cord or retinal ischemia, with clinical symptoms and without imaging evidence of acute infarction, and typically lasting less than one hour (Easton et al, 2009, Sorenson, 2011, Sacco 2013)

Notable Updates in CSBPR *Secondary Prevention of Stroke* 2017

The 2017 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.

Highlights of significant updates and new additions to the Secondary Prevention of Stroke best practice recommendations for 2017 that are based on new and emerging evidence include:

- ✓ addition of a framework for providing stroke prevention services, and a detailed list of care elements that should be included to distinguish stroke prevention services;
- ✓ revisions to the recommendations for the triage and assessment of risk of recurrent stroke after TIA/minor stroke and suggested urgency levels for investigations and initiation of management strategies (Section 1);
- ✓ smoking cessation has been added to the lifestyle section rather than a separate section (Section 2);
- ✓ minor updates to blood pressure management, lipid management and diabetes and stroke sections to reflect recent clinical trial releases and guideline updates by the respective medical societies (Sections 3, 4, 5 respectively);
- ✓ refinements to stroke prevention and management of atrial fibrillation and anticoagulant use (Section 7);
- ✓ clarifications on timing for carotid interventions (Section 8);;
- ✓ antithrombotic management in people with cervicocephalic artery dissection
- ✓ With the recent completion of the REDUCE and CLOSE trials, and long-term follow-up from the RESPECT trial, the recommendations for people with patent foramen ovale have been updated (Section 9).
- ✓ Heart failure has been added to the Cardic Issues section (Section 9)
- ✓ updates to Heart and Stroke *Taking Charge* patient information on best practices related to stroke prevention.
- ✓ updates to Heart and Stroke public information on risk factors for heart disease and stroke http://www.heartandstroke.ca/-/media/pdf-files/iavc/health-information-catalogue/en-are-you-at-risk.ashx?la=en&hash=91D622380B55E55ADB31E7ECE37C9F51BCD26D97
- ✓ updates to the HSF Stroke Assessment and Prevention Pocket Guide to align with all updates to the recommendations in this module http://www.strokebestpractices.ca/wp-content/uploads/2017/07/002-17_CSBP_StrokeAssessPocketGuide_7.5x4.25_EN_v6_LR.pdf;
- ✓ **Sleep Apnea and Stroke Prevention:** Sleep apnea is a recognized risk factor for stroke, and a condition that appears in some patients both before and following a stroke. However, the recently released findings of the SAVE trial (2016) has demonstrated that although treatment with CPAP of moderate-to-severe sleep apnea in patients with a history of coronary and cerebrovascular disease is associated with benefits including reduced daytime sleepiness and improved health-related quality of life, there is insufficient evidence to recommend CPAP

for secondary stroke prevention, and we do not recommend routine screening of patients with stroke for OSA. In light of the SAVE results, sleep apnea screening and treatment are no longer routinely recommended for secondary prevention of stroke and accordingly have removed recommendations for universal screening and treatment in stroke patients. Screening and treatment for sleep apnea symptoms should be performed as part of routine primary care based on the presence or absence of sleep apnea symptoms, as is currently done for patients without stroke.

Emerging Trends in Stroke Prevention Research

A key tenant to stroke prevention is knowing one's risk for stroke. A sizeable list of modifiable and non-modifiable risk factors for stroke has been amassed (Goldstein, Bushnell, Adams et al, 2011). Of these risk factors, family history, or genetic predisposition, is considered one of the most important risk factors. However, despite numerous epidemiological studies providing evidence for a genetic component to stroke (Flossmann, Schulz and Rothwell, 2004), the extent of this predisposition is largely unknown (Dichgans, 2007). Moreover, genetic predisposition to stroke may act at several levels by: (1) contributing to standard risk factor that have a known genetic component such as hypertension or diabetes; (2) interacting with environmental factors; (3) contributing directly to an intermediate phenotype such as atherosclerosis; or (4) affecting latency to stroke, infarct size or stroke outcome (Dichgans, 2007). Clearly, the quest to identify the underlying molecular mechanisms contributing to stroke risk has been challenging at best (Traylor M, Farrall M, Holliday EG, et al, 2012).

Recent studies examining genetic risk factors for stroke found genetic predisposition to stroke to vary based on age and stroke subtype (Flossmann, Schulz and Rothwell, 2004; Jerrard-Dunne, Cloud, Hassan and Markus, 2003; Jood, Ladenvall, Rosengren, Blomstrand and Jern, 2005; Schulz, Flossmann and Rothwell, 2004). A meta-analysis of genome-wide associations studies undertaken by the METASTROKE Collaboration confirmed that although genetic variants were detected in patients with ischemic stroke when compared to controls, all genetic variations were specific to a stroke subtype (Traylor M, Farrall M, Holliday EG, et al, 2012). The METASTROKE Collaboration posited the implications of their findings were twofold: (1) to maximize success of genetic studies in ischemic stroke, detailed stroke subtyping is required; and (2) different genetic pathophysiological mechanisms appear to be associated with different stroke subtypes, possibly leading to pharmacotherapy having different effects in different stroke subtypes. Moving forward, detailed subtyping may be required to illustrate differing effect of pharmacological profiles in secondary stroke prevention. In addition, inherited single-gene disorders can also lead to abnormalities that predispose persons toward stroke, usually a specific sub type. For example, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) syndrome, is associated with a mutation of the NOTCH3 gene, which manifests independently of traditional stroke risk factors (Tan RY and Markus, 2015). The condition results in damage to small blood vessels, which reduces blood flow, leading to recurrent subcortical cerebral infarctions. Accordingly, stroke in younger persons should raise suspicion of the presence of one of these highly penetrant mutation, either established genes (e.g. CADASIL, Fabry) or emerging ones (e.g. COL4A2). These genetic abnormalities may be identified using next generation sequencing technology, in selected individuals.

Guideline Development Methodology:

The *Canadian Stroke Best Practice Recommendations* present high-quality, evidence-based stroke care guidelines in a standardized framework to support healthcare professionals across all disciplines. Implementation of these recommendations is expected to reduce practice variations and closing 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 twelve distinct steps to ensure a thorough and rigorous process. These include the following (details available online):

1. Establish expert interprofessional writing group for module, as well as stroke survivors and/or caregivers
2. Systematic search, appraisal and update of research literature up to September 2017
3. Systematic search and appraisal of external reference guideline recommendations
4. Update of evidence summary tables
5. Writing group review and revision of existing recommendations, development of new recommendations as required
6. Submission of proposed chapter update to the Canadian Stroke Best Practices Advisory Committee
7. Internal review of proposed chapter update. Feedback to writing group, completion of edits.
8. External review, and final edits based on feedback.
9. Update of educational materials and implementation resources
10. Final approvals, endorsement and translation of chapter
11. Public release & dissemination of final chapter update
12. Continue with ongoing review and update process.

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

Conflicts of Interest: 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. Any conflicts of interest that are declared are reviewed by the Chairs of the Best Practcices Advisory Committee and appropriate HSF staff members for their potential impact. Potential members of any writing group who have conflicts that are considered to be significant are not selected for advisory or writing group membership. Participants who have conflicts for one particular topic area are identified at the beginning of discussions for that topic, and if it is the chair, then another non-conflicted participant assumes the chair role for that discussion to ensure balanced discussions. 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 additiononal 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 2017)

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]

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Citing the Prevention of Stroke 2017 Module

Theodore Wein, M. Patrice Lindsay, Robert Cote, … David Gladstone et al, on behalf of the Secondary Prevention of Stroke Writing Group. *Secondary Prevention of Stroke Module Update 2017*. In Lindsay MP, Gubitz G, Dowlatshahi D, Harrison E, and Smith EE (Editors) on behalf of the Canadian Stroke Best Practices Advisory Committee. *Canadian Stroke Best Practice Recommendations*, 2017; Ottawa, Ontario Canada: Heart and Stroke Foundation.

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 Stroke Prevention Services

*** New for 2017***

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) 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 preventiuon 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 2017;
- to strengthen service provision and increase accountability.

FIGURE TWO: HSF-CSBPR CORE ELEMENTS OF STROKE PREVENTION SERVICES UNDERLYING FRAMEWORK

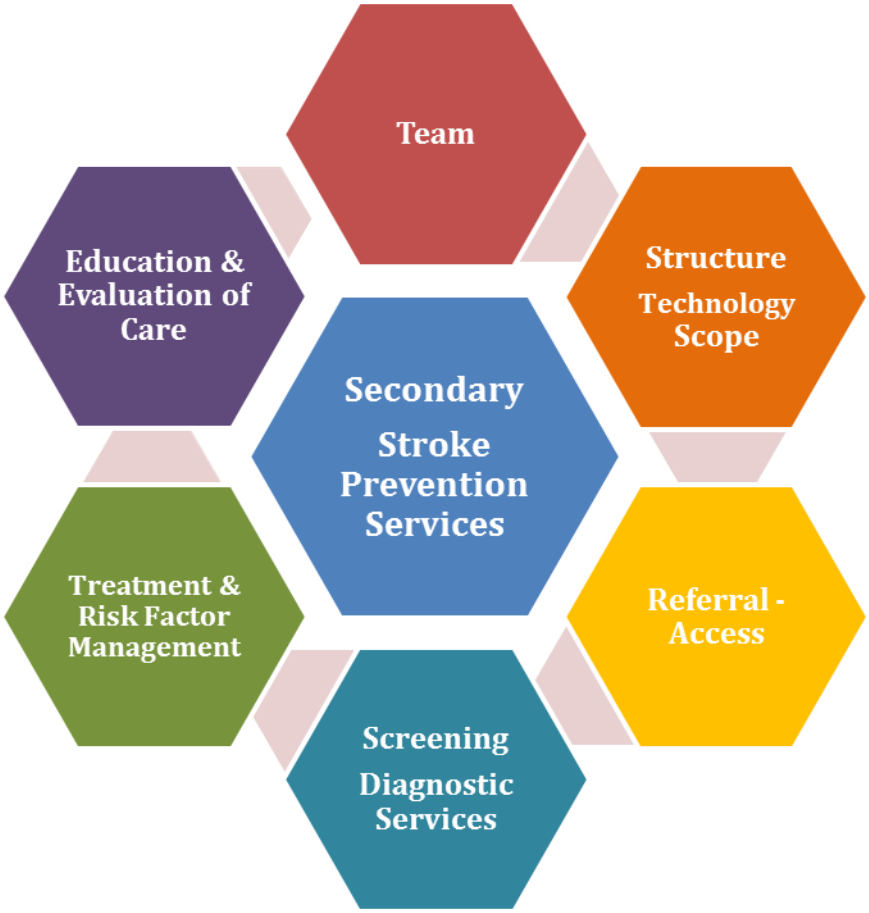

TABLE TWO: HSF CSBPR CORE ELEMENTS OF STROKE PREVENTION SERVICES

Secondary Prevention Services Core Element	Alignment with CSPBR*	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 ❑ SPS follows protocols 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 SPS provides any combination of emergent (same day), urgent (within 24 hours); semi-urgent (within 2 weeks), less

		urgent (within one month) stroke prevention services ❑ SPS are accessible to stroke and TIA patients with disabilities (e.g. physical, cognitive, and perceptual) ❑ 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, neuropsychology, nursing, rehabilitation therapy (such as physiotherapy, occupational therapy, speech-language pathology), support services (such as stroke navigator, social worker, dietician, pharmacist, administrative), research, community liaisons ❑ 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	❑ 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 ❑ SPS defines its role as providing at minimum a one-time assessment; or additionally assessment and short-term follow-up; long-term follow-up; collaborative care with primary care practitioner
Referral Mechanisms	SPOS Section 1 PHEDSC Sections 1, 3	❑ 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 ❑ SPS is aware of, andin 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 ❑ SPS follows the CSBPR target times for referrals and responds appropriately based on degree of urgency ❑ SPS monitors wait times from referral to first assessment appointment ❑ 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	Telestroke Section 1	❑ The prevention service considerstelestroke technology to increase access to services for patients living in rural and remote settings without local access to stroke specialists
Access to Diagnostic	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

Services	PHEDSC Sections 1, 3	monitoring, echocardiogram, laboratory services); ❑ Agreements are in place with diagnostic departments to access services on a more urgent basis when required as per CSBPR target times (same day, 24 hour, one week etc) ❑ 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 outside CSBPR target times
Care Delivery Elements of Stroke Prevention Services		
Screening and Assessment	SPOS; PHEDSC; 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 (such as screening tools for blood pressure, stroke severity, physical functioning, depression, cognition, atrial fibrillation, bleeding risk, lipids, diabetes, smoking, recreational drug use, other underlying cardiac issues, lifestyle behaviours, weight, fatigue, birth control and hormone replacement therapy) ❑ HSF Post-Stroke Checklist available to support screening of patients*(add Hyperlink to PSC)* ❑ Protocols in place for use of validated tools to support assessment and diagnosis ❑ Process for comprehensive assessment of vascular risk factors and potential comorbidities for patients identified as potential increased stroke risk during screening ❑ 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; PHEDSC; MCF	❑ Diagnosis should specify the type of stroke/TIAthe patient has experienced (i.e., ischemic or hemorrhagic, and if later whether subarachnoid or intracranial hemorrhage) ❑ Underlying etiology should be determined 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/TIA 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
Communication and Continuity		❑ Communication with referring physicians, primary care practitioners 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 routinelyprovides verbal education to patients and families ❑ SPS provides written and electronic educational resources (such as HSF Your Stroke Journey) ❑ SPS assesses patient and family 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, and if required available in other languages ❑ 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 ❑ Able to initiate appropriate referrals for home care support services, specialized equipment, and process for driving assessment as required
Outcome and Quality Elements of Stroke Prevention Services		
Quality and Accountability	All modules	❑ 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 ❑ SPS has a process for reporting data to staff, funders and patients ❑ SPS compares performance to pre-set targets and benchmarks and engages in quality improvement initiatives to achieve targets and readjust as appropriate. ❑ 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; PHEDSC – Pre-hospital and Emergency Department stroke 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 2017
SECONDARY PREVENTION OF STROKE

Section Three: Secondary Prevention of Stroke Recommendations

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1. Initial Risk Stratification and Management of Non-Disabling Stroke and Transient Ischemic Attack

Secondary Prevention of Stroke **1. Initial Risk Stratification and Management**

Update 2017

Note: These recommendations (Section 1) pertain to patients with TIA or subacute, nondisabling ischemic stroke who are not candidates for hyperacute thrombolysis treatment with intravenous alteplase (tPA) or endovascular thrombectomy. For patients with suspected acute stroke that warrant hyperacute investigations to determine eligibility for thrombolysis/endovascular thrombectomy refer to Hyperacute Stroke Care recommendations.

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

1.1 Timing of Initial Assessment

(Please refer to Table Three below for summary of Stroke Risk Levels and Actions)

1.1.1 VERY HIGH Risk for Recurrent Stroke (Symptom onset within last 48 Hours)

i. Patients who present **within 48 hours** of a suspected transient ischemic attack or nondisabling ischemic stroke with the following symptoms are **considered at highest risk** of first or recurrent stroke:

   a. transient, fluctuating or persistent unilateral weakness (face, arm and/or leg) [Evidence Level B];

   b. transient, fluctuating or persistent speech disturbance/aphasia [Evidence Level B];

   c. fluctuating or persistent symptoms *without motor weakness or speech disturbance* (eg. hemibody sensory symptoms, monocular vision loss, hemifield vision loss, +/- other symptoms suggestive of posterior circulation stroke such as binocular diplopia, dysarthria [Evidence Level B].

ii. Patients identified as highest risk should be ***immediately*** sent to an emergency department with capacity for advanced stroke care (such as brain imaging on site, and ideally access to acute stroke treatments) [Evidence Level C] *Refer to Section 1.2 for more information on investigations.*

iii. Urgent brain imaging (CT or MRI) and non-invasive vascular imaging (CTA or MRA from aortic arch to vertex) should be completed as soon as possible **within 24 hours** [Evidence Level B]. *Refer to Section 1.2 for more information on investigations*.

iv. An electrocardiogram should be completed without delay [Evidence Level B].

1.1.2 HIGH Risk for Recurrent Stroke (Symptom onset between 48 Hours and 2 weeks)

i. Patients who present **between 48 hours and 2 weeks** from onset of a suspected transient ischemic attack or nondisabling ischemic stroke with symptoms of transient, fluctuating or persistent unilateral weakness (face, arm and/or leg), or speech disturbance/aphasia are considered at higher risk for first or recurrent stroke [Evidence Level B].

ii. These patients should receive a comprehensive clinical evaluation and investigations by a healthcare professional with stroke expertise as soon as possible [Evidence Level B]**, ideally initiated within 24 hours** of first contact with the healthcare system [Evidence Level C]. *Refer to Section 1.2 for more information on investigations.*

1.1.3 MODERATE (INCREASED) Risk for Recurrent Stroke (Symptom onset between 48 Hours and 2 weeks)

i. Patients who **present between 48 hours and 2 weeks** of a suspected transient ischemic attack or nondisabling ischemic stroke with transient, fluctuating or persistent symptoms *without unilateral motor weakness or speech disturbance* (e.g. withhemibody sensory symptoms, monocular vision loss, binocular diplopia, hemifield vision loss, or ataxia) may be considered at increased risk of recurrent stroke [Evidence Level C].

ii. These patients should receive a comprehensive clinical evaluation and investigations by a healthcare professional with stroke expertise as soon as possible [Evidence Level B], ideally within 2 weeks of first contact with the healthcare system [Evidence Level C]. *Refer to Section 1.2 for more information on investigations.*

1.1.4 LOWER Risk for Recurrent Stroke (Time lapse since symptom onset greater than 2 weeks)

i. Patients **presenting more than 2 weeks** following a suspected transient ischemic attack or nondisabling ischemic stroke, may be considered as being less urgent, and should be seen by a neurologist or stroke specialist for evaluation, ideally within one month of symptom onset [Evidence Level C]. *Refer to Section 1.2 for more information on investigations.*

1.2 Diagnostic Investigations

1.2.1 Initial Assessment:

i. Patients presenting with suspected acute or recent transient ischemic attack or nondisabling ischemic stroke should undergo an initial assessment that includes brain imaging, non-invasive vascular imaging (including carotid imaging),12-lead ECG, and laboratory investigations.

   a. Brain imaging (CT or MRI) and non-invasive vascular imaging (CTA or MRA from aortic arch to vertex) should be completed within time frames based on triage category above [Evidence Level B]. *Refer to Table Three.*

   b. CT angiography including extracranial and intracranial vasculature 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].

   c. Vascular imaging is recommended to identify significant symptomatic extracranial carotid artery stenosis for which patients should be referred for possible carotid revascularization [Evidence Level A].

   d. Carotid ultrasound (for extracranial vascular imaging) and MR angiography are

acceptable alternatives to CTA, and selection should be based on immediate availability, and patient characteristics [Evidence level C].

ii. The following laboratory investigations should be routinely considered for patients with transient ischemic attack or nondisabling ischemic stroke as part of the initial evaluation:

a. **Initial bloodwork**: haematology (complete blood count), electrolytes, coagulation (aPTT, INR), renal function (creatinine, e-glomerular filtration rate), random glucose or hemoglobin A1c, and troponin [Evidence Level C]. *Refer to Table Four for full list of recommended lab tests.*

b. **Subsequent** laboratory tests may be considered during patient encounter or as an outpatient, including a lipid profile (fasting or non-fasting); and, screening for diabetes with either a fasting plasma glucose, or 2-hour plasma glucose, or glycated hemoglobin (A1C), or 75 g oral glucose tolerance test [Evidence Level C]. *Refer to Diabetes Canada Guidelines for further information (Link)*

iii. Patients with suspected transient ischemic attack or ischemic stroke should have a 12-lead ECG to assess cardiac rhythm and identify atrial fibrillation or flutter or evidence of structural heart disease (e.g. myocardial infarction, left ventricular hypertrophy) [Evidence Level B].

iv. For patients being investigated for an acute embolic ischemic stroke or TIA, ECG monitoring for more than 24 hours 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].

Clinical Considerations:

i. MRI is superior to CT scan in terms of diagnostic sensitivity for transient ischemic attack, and may provide additional information that could guide diagnosis, prognosis, and management decision-making. Decisions regarding MRI scanning should be based on MRI access, availability and timing of appointments.

1.2.2 Additional Investigations for Embolic Stroke of UndeterminedSource (ESUS)

i. For patients being investigated for an acute embolic ischemic stroke or TIA of undetermined source *whose initial short-term ECG monitoring does not reveal atrial fibrillation* but a cardioembolic mechanism is suspected, prolonged ECG monitoring for at least 2 weeks is recommended to improve detection of paroxysmal atrial fibrillation in selected patients aged ≥ 55 years who are not already receiving anticoagulant therapy but would be potential anticoagulant candidates [Evidence Level A]. *Refer to the Canadian Cardiovascular Society 2016 Atrial Fibrillation Guideline for additional information. Refer to Section 7 in this module on Management of Atrial Fibrillation in Stroke for additional information.*

ii. Echocardiography should be considered in cases where a stroke mechanism has not been identified [Evidence Level C].

1.3 Functional Assessment:

i. Selected patients with transient ischemic attack or ischemic stroke should be assessed for neurological impairments and functional limitations when appropriate (e.g., cognitive evaluation, screening for depression, screening of fitness to drive, need for potential rehabilitation therapy, and assistance with activities of daily living), especially for patients who are not admitted to hospital [Evidence Level B]. *Refer to Rehabilitation Module Recommendations 5.1 and 5.6 for additional information.*

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

TABLE Three: Summary of HSF Recurrent Stroke Risk Levels and Initial Management

(Based on CSBPR Secondary Prevention of Stroke, Section One: Initial Risk Stratification and Management)

Risk For Recurrent Stroke	Time from Stroke Symptom Onset to Healthcare Presentation	Presenting Symptoms	When Patients Should be Seen by Healthcare Professional	Where Patients Should be Seen	Tests to be Done on Initial Assessment
Very HIGH RISK	Within 48 hours	- Transient, fluctuating or persistent unilateral weakness (face, arm and/or leg) - Transient, fluctuating or persistent speech disturbance /aphasia. - Fluctuating or persistent symptoms **without motor weakness or speech disturbance** (eg. hemibody sensory symptoms, monocular visual loss, hemifield visual loss, +/- other symptoms suggestive of posterior circulation stroke such as diplopia, dysarthria, and/or ataxia).	Immediately	Emergency Department [ideally ED with brain imaging onsite and access to alteplase (tPA)]	CT/CTA or MRI/MRA (aortic arch to vertex), ECG, Lab Work (Table 3)
HIGH RISK	Between 48 hours and 2 weeks	- Transient, fluctuating or persistent unilateral weakness (face, arm and/or leg), or speech disturbance/aphasia	As soon as possible, ideally within 24 hours	Stroke Prevention Clinic with Neurologist or Stroke Specialist, Nurse Practitioner	CT/CTA or MRI/MRA (aortic arch to vertex), ECG, Lab Work (Table 3)
Moderate (INCREASED) RISK	Between 48 hours and 2 weeks	- Fluctuating or persistent symptoms ***without motor weakness*** or speech disturbance (e.g., hemibody sensory symptoms, monocular vision loss, binocular diplopia, hemifield vision loss, or ataxia)	As soon as possible, ideally within 2 weeks	Stroke Prevention Clinic with Neurologist or Stroke Specialist, Nurse Practitioner	CT/CTA or MRI/MRA (aortic arch to vertex), ECG, Lab Work (Table 1)
LOWER RISK	More than 2 weeks	- Any typical or atypical symptoms of stroke or transient ischemic attack	Ideally within 1 month	Ambulatory Clinic with access to Neurologist or Stroke Specialist, Nurse Practitioner	As appropriate based on assessment by healthcare team

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 12 to 20 percent within 90 days, and the risk is "front-loaded", with half of the strokes occurring in the first two days following initial symptom onset. 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 recent 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 TIA clinics.(**N Engl J Med 2016;374:1533-42)**

System Implications

- Education for the public and healthcare providers (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. Patients and families will also require ongoing education and support related to prevention and management of stroke and its associated risk factors.
- Education and training for physicians 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.
- 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.
- Well-established and accessible stroke prevention clinics, or broader vascular prevention programs available in all communities through traditional or technological means. Promotion of programs with healthcare practitioners. These resources should be listed, easily accessible to primary care physicians and healthcare providers, and updated annually.
- 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 give to community and individual barriers as well as motivators and enablers.
- Any suspicion of ischemic stroke in a child warrants an emergent consult or assessment in a pediatric emergency department. All hospitals should have a referral process established with the closest specialized pediatric facility.

Performance Measures

1. Proportion of acute stroke and TIA 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 TIA 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, CT or MR angiography); and electrocardiogram.

6. ***Developmental KQI:*** *Proportion of HIGHEST risk TIA 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 also apply applicable to this recommendation but are not repeated here.

Implementation Resources and Knowledge Transfer Tools

Health Care Provider Information

- HSF Stroke Assessment and Prevention Pocket Cards 2016. Hard copy available through HSF order form
- HSF Stroke Assessment Pocket Cards http://www.strokebestpractices.ca/wp-content/uploads/2017/07/002-17_CSBP_StrokeAssessPocketGuide_7.5x4.25_EN_v6_LR.pdf
- Canadian Stroke Best Practice Recommendations Hyperacute Care Module: Table 3.1: Screening and Assessment Tools for Acute Stroke Severity
- Canadian Cardiovascular Society Atrial Fibrillation Guidelines 2014 Focused Update: Management of Atrial Fibrillation http://www.onlinecjc.ca/article/S0828-282X(14)01249-5/pdf
- American College of Chest Physicians (ACCP), Antithrombotitc Therapy for VTE Disease: CHEST Guideline and Expert Panel Report http://journal.publications.chestnet.org/article.aspx?articleid=2479255

  This CHEST guideline addresses new developments and ongoing controversies in the treatment of VTE.
- Canadian Association of Radiologists 2012pracitce guidelines: http://www.car.ca/en/standards-guidelines/standards.aspx
- Canadian Neurological Scale: https://www.strokengine.ca/assess/cns/

Patient Information

- Signs of stroke: http://www.heartandstroke.ca/stroke/signs-of-stroke
- Stroke information: http://www.heartandstroke.ca/stroke/what-is-stroke
- Atrial Fibrillation information: http://www.heartandstroke.ca/heart/conditions/atrial-fibrillation
- Your Stroke Journey: http://www.strokebestpractices.ca/wp-content/uploads/2015/03/YOURSTROKEJOURNEY.FINAL_.ENGLISH..pdf
- Post -Stroke Checklist: http://www.strokebestpractices.ca/wp-content/uploads/2014/06/HSF%20Post%20Stroke%20Checklist_WEB.pdf
- HSF Risk Factors for Heart DIsease and Stroke (new 2017) http://www.heartandstroke.ca/-/media/pdf-files/iavc/health-information-catalogue/en-are-you-at-risk.ashx?la=en&hash=91D622380B55E55ADB31E7ECE37C9F51BCD26D97

Summary of the Evidence 2017

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. More recently, 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 recurrent stroke in 2.6% of patients within 7 days and 3.9% within 90 days among 1,137 patients admitted to 30 centers in Spain, presenting with TIA. 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: over time 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.

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 results, which included 4,583 patients recruited from 61 sites in 21 countries from 1997-2003, have recently become available (Amarenco et al. 2016). In terms of stroke etiology, 5.0% of the 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.

Several tools are available to assess the likelihood of recurrent stroke in patients presenting with TIA. After assessing 8 assessment tools, Purroy et al. (2012) reported that ABCD3 and ABCD3V were the best predictors of stroke at 7 and 90 days. The corresponding areas under the curve (AUC) were 0.66 ($p=0.004$) and 0.69 ($p<0.001$) at day 7 and 0.61 ($p=0.015$) and 0.63 ($p=0.003$), at day 90. All other tools, including the California Risk Score, ABCD, ABCD2, ABCDI, ABCD2I, SPI-II and ESRS were unable to predict stroke risk beyond chance alone ($p>0.05$) at either day 7 or 90. Perry et al. (2014) identified 13 independent predictors of stroke recurrence within 7 days and used them to develop the Canadian TIA Score. The AUC for this tool was 0.77 (95% CI 0.73-0.82). The strongest predictors of stroke were established antiplatelet therapy, initial diastolic blood pressure ≥110 mm Hg, and initial blood glucose ≥15 mmol/L. Coutts et al. (2012) reported that for patients with TIA or minor stroke, a CT/CTA performed within 24 hours was predictive of recurrent stroke at 90 days. In fact, a positive CT/CTA was the only clinical or imaging parameter that remained a significant predictor identified in multivariable analysis.
It remains unclear whether there are differences in progression to stroke associated with different models of care. Neither Paul et al. (2013), nor Martinez-Martinez et al. (2013) reported significant differences in recurrent stroke following TIA in patients who were managed in outpatient clinics or hospital settings, although both authors noted that the costs were significantly increased (up to 5-fold) when patients were managed in hospital. Giles & Rothwell (2007) reported that the risk of recurrent stroke varied considerably depending on the clinical setting, with the lowest risk associated with specialized stroke services, where stroke recurrence was only 0.6% at day 2 and 0.9% at day 7. Patients who have immediate access to

services that offer diagnostic testing such as imaging achieve better outcomes. Rothwell et al. (2007) found that immediate access to a stroke unit and timely initiation of prophylactic medication resulted in both fewer recurrent strokes and adverse events for patients compared to patients who had a lengthier delay in receiving this care.

Detecting atrial fibrillation (AF) after a stroke or TIA is important since it is a major risk factor for subsequent stroke and, once identified, can be effectively treated. However, AF is under-diagnosed because it is frequently paroxysmal and asymptomatic, and patients do not routinely undergo prolonged screening. The 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. The results from four RCTs and numerous observational studies have demonstrated that prolonged post-stroke ECG monitoring using wearable or insertable devices is effective for improving the detection of paroxysmal AF (number needed to screen range from 8-14), with longer monitoring durations associated with an increased probability of AF detection. In the Event Monitor Belt for Recording Atrial Fibrillation after a Cerebral Ischemic Event (EMBRACE) trail (Gladstone et al. 2014), a 30-day ambulatory cardiac event monitor was found to be superior to repeat 24-hour Holter monitoring in identifying AF in 572 patients aged 52 to 96 years (mean=72.5 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 in 16.1% of patients, using the cardiac event monitor compared with 3.2% of patients in the Holter group (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. In a UK trial (Higgins et al. 2013) in which 100 patients with no history of AF and in sinus rhythm were randomized, a strategy of 7-day ECG monitoring in the acute phase post-stroke was found to be 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. The Finding Atrial Fibrillation in Stroke - Evaluation of Enhanced and Prolonged Holter Monitoring (FIND-AF) trial randomized 398 patients over age 60 years (average age 73 years) reported that a strategy of 10-day Holter monitoring started within the first week post stroke and repeated at 3 months and 6 months was superior to standard care, which consisted of an average of 73 hours of inpatient telemetry plus an average of 24 hours of Holter monitoring (Wachter et al. 2016). At 6 months, detection of AF was significantly higher in the prolonged monitoring group (13.5% vs. 4.5%; absolute difference 9%, 95% CI 3.5-14.6, p=0.002; NNS=11). Similar findings were reported in the Cryptogenic Stroke and Underlying AF (CRYSTAL-AF) trial (Sanna et al. 2014) when patients (mean age of 61.5 years) received long-term monitoring with an insertable cardiac monitor (ICM). At 6 months, the rate of detection of AF was significantly higher among patients assigned to the ICM group (8.9% vs. 1.4%, HR=6.4, 95% CI 1.9- 21.7,

p<0.001), compared with those who received standard monitoring using ECG monitoring on a schedule at the discretion of their treating physician. Similar results were reported at 12 months (12.4% vs. 2.0%, HR=7.3, 95% CI 2.6- 20.8, p<0.001).
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 and may lead to a change in patient management from antiplatelet to anticoagulant therapy, there are notable limitations to the available evidence, as 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.

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.

Initial Triage and Evaluation Evidence Tables and Reference List

TABLE Four: 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 TIA. Patient presentation, clinical judgment, and local stroke protocols should be considered in selecting appropriate laboratory investigations and the timing of completion.

Initial Recommended Laboratory Investigations for Patients with Stroke and TIA			
Complete Blood Count (CBC)	International Normalized Ratio (INR)	Partial Thromboplastin Time (PTT)	Random Glucose or Hemoglobin A1C
Electrolytes	Creatinine/eGFR	ALT	Troponin
Follow-up Blood work: to be completed as soon as possible after initial bloodwork once patient has fasted for an appropriate amount of time.		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 individual 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 x 3 (per individual institutional protocol)
Blood and/or urine drug screen	HIV, syphilis serology	

Coagulopathy Screen – For consideration in selected patients *only if clinically indicated* *Recommend consultation with a specialist in thrombosis to evaluate for hypercoagulable state*			
Anticardiolipin (Antiphospholipid) antibody	Lupus anticoagulant	Sickle cell screen	Homocysteine (fasting serum level)

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*	
Consider LP for CSF analysis (cell count and differential, protein, glucose, bacterial and viral cultures; 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 Behavioursand Risk Factor Management

Secondary Prevention of Stroke 2. Lifestyle Behavioursand Risk Factor Management

Update 2017

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

2.0 Risk Factor Assessment:

i. Persons at risk of stroke and patients who have had a stroke 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 should receive individualized information and counseling about possible strategies to modify their lifestyle and risk factors [Evidence Level B].

iii. Referrals to appropriate specialists should be made where required [Evidence Level B].

   a. The specialists may provide more comprehensive assessments and structured programs to manage specific risk factors [Evidence Level B].

2.1 Healthy Balanced Diet:

i. Counsel and educate individuals with TIA or stroke to eat a healthy balanced diet that includes:

   a. a variety of natural/whole foods at each meal [Evidence Level B].

   b. fewer highly processed foods which include highly refined foods, confectionaries, sugary drinks, processed meats, and snack foods [Evidence Level B].

   c. a diet high in vegetables and fruit; encourage patients to choose fresh or frozen unsweetened fruit, or fruit canned in water without added/free sugars or artificial/non-caloric sweeteners; fresh or frozen vegetables without added sauce, or canned vegetables with no added salt [Evidence Level B].

   d. fat-free or skim milk and alternatives, and dietary and soluble fibre [Evidence Lebel B].

   e. lean meats, whole grains and protein from plant sources which are low in saturated and trans fats, low in cholesterol (< 200 mg daily for patients at increased vascular risk) and low in sodium [Evidence Level B].

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

iii. Counsel and educate individuals with TIA or stroke to have a total intake of free sugars that does not exceed 10% of total daily calorie (energy) intake [Evidence Level B]

   Note: While sugar is a problematic part of our diet, sugar in liquid beverage form is of particular concern. Sugary drinks that may include soft drinks, juice, vitamin waters and sports drinks are considered energy-dense, nutrient poor beverages because of their high caloric levels and minimal nutritional value. Heart & Stroke Position Statement on Sugary Drinks 2016

2.2 Sodium Intake:

i. Counsel and educate individuals with TIA or stroke to have a daily sodium intake from all sources to no more than 2,000 mg per day [Evidence Level A]. *Refer to the CHEP 2016 for additional information.*

2.3 Exercise:

i. Counsel and educate individuals with TIA or stroke to reduce sedentary behaviours and to work towards increased activity goals as tolerated throughout their stroke recovery [Evidence Level B].

ii. Counsel and educate individuals with TIA or stroke to participate in dynamic exercise of moderate intensity (such as brisk walking, jogging, swimming, cycling) 4 to 7 days per week, to accumulate at least 150 minutes in episodes of 10 minutes or more, in addition to routine activities of daily living *(Refer to the CSEP Canadian Physical Activity Guidelines 2011 and CHEP 2015 for additional information)* [Evidence Level B].[4]

iii. Most people who have had a stroke or TIA should be encouraged to start a regular exercise program [Evidence Level C].

a. 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, or in individuals with other comorbid disease (such as cardiac disease), which may place them at higher risk of medical complications [Evidence Level C].

2.4 Weight:

i. Counsel and educate individuals with TIA or stroke to achieve a body mass index (BMI) of 18.5 to 24.9 kg/m^2; or a waist circumference of <88 centimetres for women and <102 centimetres for men* [Evidence Level B]. *(*Note: these numbers are reflective of current research based mostly on Caucasian patients. Refer to Reference list for waist circumference values for other ethnic groups)*

ii. Counsel and educate individuals with TIA or stroke who are overweight to set healthy weight loss goals and develop individualized plans to achieve goals [Evidence Level B].

a. Referral to dietitian should be considered (Evidence Level B].

2.5 Alcohol consumption:

i. Counsel and educate individuals with TIA or stroke to avoid heavy alcohol use as excessive alcohol intake increases the risk of ischemic stroke and intracranial hemorrhage. [Evidence Level B].

ii. Counsel and educate individuals with TIA or stroke to follow Canada's Low-Risk Alcohol Drinking Guidelines (2011): 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 C].

Note: one standard drink is considered to be 13.6 g or 17.2 ml of ethanol, or approximately 44 mL of 80 proof (40%) spirits, 355 mL of 5% beer or 148 mL of 12% wine.

2.6 Oral Contraceptives and Hormone Replacement Therapy:

i. Estrogen-containing oral contraceptives or hormone replacement therapy should be discouraged or discontinued in female patients with TIA or ischemic stroke [Evidence Level B]. Management alternatives should be considered in these patients [Evidence Level C].

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 if not prescribed for medical

indications [Evidence Level C]; and should be provided with appropriate support and referrals to services and resources for drug addiction and rehabilitation [Evidence Level B].

2.8 Smoking Cessation

Note, the term 'Smoking' in these recommendations refers to tobacco and other inhaled substances. These recommendations are applicable to stroke of ischemic and hemorrhagic origin.

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. 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.*

v. A combination of pharmacological therapy 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, and patient preferences [Evidence Level C]. *Refer to Appendix Three: Pharmacotherapy in Smoking Cessation Treatment.*

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].

2.9 Adherence to Individual Prevention Plans

i. At each stroke prevention visit with healthcare team members, assess patients for adherence to individualized secondary prevention plans (pharmacotherapy and lifestyle changes) [Evidence Level C].

Note: Adherence topics include medication compliance; diet management, rehabilitation therapy and/or exercise participation, and other areas specific to each patient.

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.

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. Obesity may be result of an obesegenic 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).

Regular exercise also reduces the risk of stroke and other vascular diseases.[5]Research has demonstrated an increased risk of thrombosis with estrogen-based hormone therapy (both oral contraceptives and hormone-replacement therapy).

Although causes of stroke are generally different for children, lifestyle management issues as described above are equally as important for the paediatric population, particularly as the long-term risk of recurrence for children is much higher.

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 CAN-ADAPTT working group has reported that approximately 17% of Canadians 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.

System Implications

- Health promotion efforts that contribute to the prevention of stroke in all communities (integrated with existing chronic disease prevention initiatives) must be established.
- 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.
- Public and population health focus on cerebrovascular health for paediatric casesfocus on risk reduction through diet, - including limited fat, sodium and sugar intake,- exercise, non-smoking, avoidance of drugs that increase stroke risk.
- 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
- 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.
- Local, regional and federal food strategies which improve access to whole unprocessed foods in all communities.
- Access to risk factor management programs (such as hypertension and smoking cessation programs) in all communities, primary healthcare settings and workplaces.
- Improved access to best practice cessation support through pharmaceuticals, nicotine replacement theraphy and behavior counseling through private and public drug coverage plans.
- Government action at all levels of government to reduce tobacco use. Use WHO MPOWER

tobacco control strategy.

- 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.
- 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.
- Improved access to pharmaceuticals and behavior counseling for smoking cessation through private and public drug coverage plans.
- Government action at all levels of government to reduce tobacco use.
- Government regulation of e-cigarettes, including prohibiting e-cigarette sales to minors, 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; and restriction of e-cigarette advertising and promotion.
- Access to culturally and ethnically appropriate educational resources in multiple languages as well as special resources for patients with aphasia.
- Increased active infrastructure in communities to ensure the built environment supports physical activity for all ages.
- Access to healthy living programs, educational materials and healthcare professionals for persons living in rural and remote locations, including innovative use of technology.

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 TIA 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 TIA 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 TIA with a history of tobacco smoking who are given smoking cessation advice and counseling during acute hospital stay, inpatient and outpatient rehabilitation, and during secondary prevention visits.
9. Proportion of stroke and TIA patients who participate in a smoking cessation program who are smoke-free at 6 months, one year and two years.

Measurement notes

- 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.

- Performance measures 4: administrative data are available at the local, provincial and national levels.
- Mortality rates should be risk adjusted for age, sex, stroke severity and comorbidities.

Implementation Resources and Knowledge Transfer Tools

Health Care Provider Information

- How to take a proper waist measurement: http://www.heartandstroke.on.ca/site/c.pvI3IeNWJwE/b.4018281/k.8698/Healthy_Waists.htm
- Eat Well and Be Active Education Toolkit: http://www.hc-sc.gc.ca/fn-an/food-guide-aliment/educ-comm/toolkit-trousse/index-eng.php
- Recommended intake for sodium table:http://www.hc-sc.gc.ca/fn-an/nutrition/sodium/index-eng.php#a2)
- Sugar position statement http://www.heartandstroke.ca/-/media/pdf-files/canada/2017-position-statements/sugar-ps-eng.ashx
- Canadian Physical Activity Guidelines for Adults 18-64 years old. http://www.csep.ca/CMFiles/Guidelines/CSEP_PAGuidelines_adults_en.pdf
- Canadian Physical Activity Guidelines for Older Adults 65 years and older - http://www.csep.ca/CMFiles/Guidelines/CSEP_PAGuidelines_adults_en.pdf
- *Canadian Best Practice Recommendations for Stroke Care* Smoking Cessation Pharmacology Summary Table: http://www.strokebestpractices.ca/wp-content/uploads/2013/03/Table1_Smoking_EN.pdf
- Canadian Smoking Cessation Clinical Practice Guideline:

  https://www.nicotinedependenceclinic.com/English/CANADAPTT/Pages/Home.aspx
- Smoking Cessation and the Cardiovascular Specialist: Canadian Cardiovascular Society Position Paper. http://www.onlinecjc.ca/article/S0828-282X(10)00076-0/fulltext
- Ottawa Model for Smoking Cessation: http://www.ottawamodel.ca/en_about-TheOMSC.php
  - E-learning, workshops and other resources: http://www.ottawamodel.ca/en_education.php
- CADTH Smoking Cessation Pharmacology

  https://www.cadth.ca/pharmacologic-based-strategies-smoking-cessation-clinical-and-cost-effectiveness-analyses
- CAMH Nicotine Dependance Clinic
- http://knowledgex.camh.net/primary_care/toolkits/addiction_toolkit/smoking/Pages/tools_resources.aspx
- CAN-ADAPTT Tools and resources:
- https://www.nicotinedependenceclinic.com/English/CANADAPTT/Pages/Tools%20and%20Resources/Guideline-Tools.aspx
- Smoking cessation e-learning and webinars: http://tobaccofreernao.ca/en
- The Change Book: http://www.nattc.org/pdf/The_Change_Book_2nd_Edition.pdf
- The Change Book Workbook: http://www.nattc.org/pdf/The_Change_Book_2nd_Edition_Workbook.pdf
- Readiness-ruler: http://www.quitlinenc.com/health-professionals/screening-brief-intervention/counseling-delivery-methods/readiness-ruler
- Contemplation ladder: http://www.nd.gov.hk/pdf/bdf-2010R2-q13-eng.pdf
- Heaviness of Smoking Index: http://www.iarc.fr/en/publications/pdfs-online/prev/handbook12/Tobacco_vol12_appendices.pdf
- The 5 A's intervention tool: http://mdquit.org/fax-to-assist/module-2

Patient Information

- Heart and Stroke resource: Are you at risk for heart disease or stroke? Take action and reduce your risk. http://www.heartandstroke.ca/-/media/pdf-files/canada/health-information-catalogue/en-are-you-at-risk.ashx?la=en&hash=66B2A7DE8A6D2D08833F3ABF065C7E36B495C338
- Eating Well with Canada's Food Guide: http://www.hc-sc.gc.ca/fn-an/food-guide-aliment/index-eng.php
- Heart and Stroke Foundation Healthy Living information: http://www.heartandstroke.ca/get-healthy
- Mediterranean diet http://www.mayoclinic.com/health/mediterranean-diet/CL00011

- My Heart&Stroke Risk Assessment: www.heartandstroke.ca/riskStroke prevention and risk factors: http://www.heartandstroke.on.ca/site/c.pvI3IeNWJwE/b.3581691/k.157D/Stroke__Stroke_prevention_and_risk_factors.htm
- Stroke Prevention and Risk Factors: http://www.heartandstroke.ca/stroke/risk-and-prevention
- Healthy Weight Action Plan: https://ehealth.heartandstroke.ca/HeartStroke/HWAP2/Home.aspx
- <30 Days app: http://www.heartandstroke.ab.ca/site/c.lqIRL1PJJtH/b.8173153/k.9029/Health_eTools.htm
- Smoking, heart disease and stroke: http://www.heartandstroke.com/site/c.ikIQLcMWJtE/b.3484173/k.A7AC/Stroke__Smoking.htm
- Tobacco Quit Line: 1-866-366-3667
- Break it off http://breakitoff.ca/
- Smokers Helpline online program: http://www.smokershelpline.ca/
- Health Canada Smoking Cessation: http://www.hc-sc.gc.ca/hc-ps/tobac-tabac/quit-cesser/index-eng.php
- Quit Now: https://www.quitnow.ca/
- Lung Association Journey2Quit workbook. http://www.on.lung.ca/document.doc?id=1211

Summary of the Evidence 2017

A healthy lifestyle, which includes a healthy balanced diet, exercise, weight control, reduction and avoidance of alcohol and tobacco, reduces the risk of an initial stroke and the risk of a subsequent stroke for patients with a prior history of stroke. Data from the Global Burden of Disease Study 2013 (Murray et al, 2013) were used to estimate the population-attributable fraction (PAF) of stroke-related disability-adjusted life-years (DALYs) associated with 17 potentially modifiable risk factors. While global estimates were provided, data from separate countries were also reported. Stroke burden among Canadians was attributed to a variety of modifiable risk factors, including 20% for diets low in fruits and vegetables, 13% for diets high in sodium, 11% for low levels of physical activity, 28% for a body mass index greater than 23.0, and 13% for tobacco use. These results are consistent with other reports. The recent INTERSTROKE 2 study (O'Donnell et al 2016) reported that among 10 risk factors, the odds of all stroke were 2.5 times higher among persons with a self-reported history of hypertension, 2 times higher among heavy alcohol consumers and over 1.5 times higher for tobacco smokers. The associated population attributable risk estimates were 34%, 5.8% and 12%, respectively.

Diet

Examining the relationship between stroke risk and diet is challenging, in large part due to the limitations in methods for collecting long-term dietary intake and controlling for potential confounders. The results of studies evaluating individual dietary components (fruit/vegetable consumption, fats, dairy products and whole grains) and dietary patterns of eating have yielded ambiguous results.

There is evidence to suggest that regular consumption of fruits and vegetables reduces the risk of stroke. The results from the China Kadoorie Biobank Study (Du et al. 2016) included 512,891 adults, aged 35-74 years, without a history of cardiovascular disease or treatment for hypertension. During 3.2 million person-years of follow-up, the incidences of both ischemic and hemorrhagic stroke were significantly lower among those who consumed fruit at least monthly. The reduction was dose-dependent, such that daily consumption was associated with the lowest risk for both stroke types. The Hazard Ratios for daily consumption were 0.75 (ischemic stroke) and 0.64 (hemorrhagic stroke). Data from the Global Burden of Disease Study 2013 (Feigin et al. 2016) was used to estimate the population-attributable fraction (PAF) of stroke-related disability-adjusted life-years (DALYs) associated with 17 potentially modifiable risk factors, including diets low in fruits and vegetables. While data from 188 countries was reported, country-specific estimates were also provided. In Canada, 20.4% (95% uncertainty interval 9.7%-31.5%) of the stroke burden was attributed to diets low in fruits, while 19.5% (95% uncertainty interval 14.4%-25.5%) was attributed to diets low in vegetables. In a cohort study including 175,000 participants, Sharma et al. (2013) reported no protective effect of consuming fruit or vegetables in either men or women during 8 years of

follow-up. The mean number of servings of fruit and vegetables between those who died of stroke was similar to all others, assessed by determining whether participants were compliant with the USDA's food pyramid. In a case-control study, O'Donnell et al. (2010) reported that increased consumption of fruit was associated with a decreased risk of stroke (adj OR of tertile 1 vs. 3=0.61, 99% CI 0.66-0.91), while increased consumption of vegetables was not (adj OR of T3 vs. T1=0.91, 99% CI 0.75-1.00). A meta-analysis (He et al. 2006) that included 20 studies and 760,629 participants, with follow-up ranging from 4-37 years, reported the risk of stroke was significantly lower in the groups associated with the highest intake of fruits and vegetables (Total combined fruit and veg: RR=0.79, 95% CI 0.75-0.84; Fruit: RR=0.77, 95% CI 0.71-0.84; Vegetables: RR=0.86, 95% CI 0.79-0.93). For every increase of 200 g/day of vegetables, stroke risk was decreased by 11% (RR=0.89, 95% CI 0.81-0.98). The corresponding decrease in stroke risk for fruit was 32%.

The role of dietary fat as a risk factor for stroke remains unclear. Siri-Tarino et al. (2010) conducted a systematic review & meta-analysis that included the results of 21 prospective cohort studies, of which stroke was the outcome in 8 studies (n=179,436). The mean follow-up periods ranged from 8-23 years. There was no increased risk of stroke associated with the highest intakes of saturated fat compared with the lowest (adjusted RR=0.81, 95% CI 0.62-1.05, p=0.11). Results from the Prospective cohort study *Multi-Ethnic Study of Atherosclerosis (MESA),* suggest that the source of saturated fat is a greater indicator of cardiovascular risk (De Oliveira Otto et al. 2012). While stroke was not an outcome assessed in this study, saturated fat from dairy sources was found to be protective for incident cardiovascular disease, while the risk was increased for consumption of saturated fat from meat sources. He et al. (2003) did not find significant associations between amount of total fat, source of fat (animal or vegetable), type of fat (saturated, unsaturated, monounsaturated, polyunsaturated, trans fat or cholesterol) or selected high-fat foods, including red meat, high-fat dairy products, nuts and eggs, and incidence of ischemic or hemorrhagic stroke. This prospective cohort study included data from 43,732 men aged 40-75 years from the Health Professionals' follow-up study who were free of cardiovascular disease and diabetes at baseline. The consumption of trans fat is generally thought to be associated with negative health outcomes. Using data from the REasons for Geographic And Racial Differences in Stroke (REGARDS) study, including 17,107 participants ≥45 years of age and without a history of stroke, Kiage et al. (2014) examined the relationship between incident stroke and trans-fat consumption. During a median of 7 years of follow-up, the risk of ischemic stroke was reported to be elevated significantly for men (HR=1.13, 95% CI 1.00-1.28), but not for women (HR=0.93, 95% CI 0.77-1.12).

The results from two recent systematic reviews (Hu et al. 2014, Qin et al. 2015), including the results from 15 and 22 cohort studies, respectively, suggest that dairy consumption may be protective for stroke (RR=0.80, 95% CI 0.76-0.84 and RR=0.87, 95% CI 0.77-0.99). While increased consumption of dairy products in general was associated with a lower risk of stroke, in sub group analyses the effect was most pronounced for low-fat dairy, cheese and fermented milk products. Hu et al. (2014) reported a non-linear dose-response relationship between milk consumption and stroke risk whereby 200 mL/day was most protective (RR=0.82, 95% CI 0.79-0.86). Larsson et al. (2012) also reported that consumption of low-fat dairy products was associated with a decreased risk of all stroke (RR=0.88, 95% CI 0.80-0.97) and ischemic stroke (RR=0.87, 95% CI 0.78-0.98) in a cohort study including 74,961 Swedish men and women, aged 45-83 years without a history of stroke.

In terms of reductions in stroke risk associated with different dietary patterns, Agnoli et al. (2011) compared adherence to four commonly-recognized diet regimes and their impact on stroke risk, including the Healthy Eating Index 2005 (HEI-2005), Dietary Approaches to Stop Hypertension (DASH), Greek

Mediterranean Index, and the Italian Mediterranean Index. There was an inverse relationship between adherence to each of the regimens and stroke occurrence. Overall, the Italian Mediterranean Index was the most protective (HR = 0.37, 95% CI = 0.19–0.70). A systematic review & meta-analysis was conducted by Psaltopoulou et al. (2013) to examine the protective effects associated with adherence to the Mediterranean diet. Of the 11 studies that were included that assessed stroke as an outcome, 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. The majority 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). A systematic review and meta-analysis authored by Soedamah-Muthu et al. (2013) provides evidence of the reduced risk of stroke associated with a dietary approach similar to the Mediterranean-style diet, the DASH style diet, which is characterised by fruits, vegetables, and low-fat or non-fat dairy, as well as less-refined grains. High adherence was protective for the development of cardiovascular disease (RR=0.80, 95% CI 0.74-0.86). 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.

Vitamin B supplementation to Reduce the Risk of Recurrent Stroke

Hyperhomocysteinemia has been associated with premature atherosclerosis and an increased risk of cardiovascular events, including stroke. Since low serum levels of B vitamins, including B_6, B_{12} and folic acid are associated with elevated homocysteine levels, supplementation has been examined as a potential means to reduce stroke risk. Two large trials have been published which included persons exclusively with recent stroke. In the VITAmins TO Prevent Stroke (VITATOPS) trial (Hankey et al. 2010) participants were randomized to receive B vitamins (2 mg folic acid, 25 mg vitamin B_6, and 0.5 mg vitamin B_{12}) or placebo for the duration of the trial. After a median duration of follow-up of 3.4 years, there was a borderline significant reduction in the risk of the composite outcome, which included stroke, MI and vascular death in the vitamin B group (15% vs. 17%, RR=0.91, 95% CI 0.82-1.00, p=0.05, absolute risk reduction of 1.56%, 95% CI -0.01-3.16). The risk of fatal or nonfatal stroke was not reduced significantly with vitamin supplementation (9% vs. 10%, RR=0.92, 95% CI 0.81-1.06, p=0.25). Toole et al. (2004) randomized 3,680 patients with a total homocysteine level ≥25th percentile to receive high-dose B vitamins (25 mg B_6, 0.4 mg B_{12}, and 2.5 mg folic acid) or low-dose B vitamins (200 µg B_6, 6 µg B_{12}, and 20 µg folic acid) in the Vitamin Intervention for Stroke Prevention (VISP) trial. The mean duration of follow-up was 20.3 months. There was no significant difference between groups in the relative 2-year risk of recurrent cerebral infarction (8.1% vs. 8.4%, RR=1.0, 95% CI 0.8-1.3).

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. 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 mmHg, 95% CI -5.18 to -3.18; p<0.001) and DBP (-2.06 mmHg, 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 mmHg, 95% CI -4.15 to -6.62; p<0.001) and DBP (-2.82 mmHg, 95% CI -2.11 to -3.54; p<0.001). Abuerto et al. (2013) identified 36 RCTs (n=5,508; n with hypertension=1,478) also comparing the effects of decreased sodium vs. higher sodium intake. The mean between group difference in sodium intake was ≥40 mmol/day. Reduced sodium intake was associated with a mean SBP reduction of 3.39 mm Hg (95% CI 2.46 to 4.31) in all participants and a mean SBP reduction of 4.06 mm Hg (95% CI 2.96 to 5.15) in participants with hypertension. In trials where the relative sodium reduction of subjects in the intervention group was <1/3 of the control group, there was a significant reduction in both SBP (MD= -1.45, 95% CI -2.29 to -0.60) and DBP (MD= -0.74, 95% CI -1.28 to -0.19). In trials where the relative sodium reduction of subjects in the intervention group was ≥1/3 of the control group, the reductions in both SPB and DBP were even greater (SBP: MD= -3.79, 95% CI -4.82 to -2.75 and DBP: MD= -1.68, 95% CI -2.34 to -1.02). There is evidence of a U-shaped pattern associated with sodium intake and stroke risk/mortality. Graudal et al. (2014) included the results of 23 cohort studies (n=274,683) and reported that usual daily sodium intake (115 -215 mmol) was associated with a significantly lower risk of all-cause mortality compared with low-sodium intake (<115 mmol), with no effect on stroke risk. High sodium intake (>215 mmol) was associated with an increased risk of both stroke and all-cause mortality, compared with usual sodium intake. O'Donnell et al. 2014 reported that sodium intake between 3 g (130 mmol) and 6 g (260 mmol) per day was associated with a lower risk of death and cardiovascular events than either a higher or lower level of sodium intake.

Exercise

Physical activity 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. Armstrong et al. (2015) included 1.1 million women who were participants of the Million Women Study, which investigated how various reproductive and lifestyle factors affect women's health. Women who engaged in strenuous physical activity 1-3x/week had a lower risk of both intracerebral hemorrhage and ischemic stroke compared with women who rarely or never engaged in such activity. The effect was U-shaped such that the risk of stroke was not reduced significantly for women who engaged in strenuous activity more than three times per week. In the REGARDS study, a large prospective cohort study including 30,239 US residents aged ≥45 years, McDonnell et al. (2013) reported that the risk of stroke was increased in persons who engaged in no physical activity, compared to persons who exercised ≥4x/week (HR= 1.20, 95% CI, 1.02–1.42). 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. There was a

decreased risk of total, ischemic and hemorrhagic stroke associated with regular physical activity. While Sattelmair et al. (2010) reported that increasing amount of time spent engaged in physical activity was not associated with decreased total stroke risk in 39,315 healthy women who had been participants of the Women's Health Study (1992-1995), those who walked ≥2 hours per week had a 30% lower risk of any stroke than women who did not walk (RR=0.70 95% CI, 0.52 to 0.94). Additionally, women who reported walking at a brisk pace (4.8 km/hour) had a 37% lower risk (RR=0.63, 95% CI, 0.44 to 0.91) compared with women who did not walk. Lee et al. (2003) published a meta-analysis of 23 studies published between 1983 and 2002 examining the association between physical activity and stroke incidence or mortality and reported a dose-response relationship. Highly active individuals had a 27% lower risk of stroke than individuals who were designated as "low active." Individuals who were designated as moderately active also had a significantly reduced risk of ischemic and hemorrhagic strokes when compared with low active individuals (RR = 0.80, 95% CI 0.69-0.91$p < 0.001$).

Weight

Evidence suggests 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 increase of greater than 10% over the previous five years was also associated with increased stroke risk. Bazzano et al. (2010) reported similar findings in a study of 154,736 Chinese men and women ≥ 40 years. The risk for stroke increased significantly for persons considered overweight (BMI 25.0 to 29.9, HR=1.43, 95% CI 1.36-1.52) and for those who were obese (BMI≥ of 30, HR=1.72, 95% CI 1.55-1.91). In phases 1 and 2 of the INTERSTROKE case-control study, O'Donnell et al. (2010, 2016) reported that increasing weight-to-hip ratio was associated with increased risk of total stroke, ischemic stroke and hemorrhagic stroke. Hu et al. (2007) studied 49,996 men and women aged 25-74 years with no history of stroke or coronary heart disease. BMI, waist circumference and waist-hip measures were obtained at baseline and stroke risk was assessed after an average follow up of 9.5 years. The risk of all stroke and ischemic stroke were increased in both men and women with increasing BMI, while increased waist circumference and waist-to-hip ratio were risk factors for total and ischemic stroke in men, but not women.

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. Zhang et al. (2014) used the results of 27 prospective studies including 1,425,513 adult participants to estimate this dose-response relationship. The relationship between ETOH dose and stroke risk was found to be j-shaped, with alcohol intake of 0-20 g/day associated with a significant reduction and intake above 40 g/day associated with increased risk. The association between alcohol consumption and risk of stroke may be different for men compared with women. 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, Patra et al. (2010) reported a dose-response relationship that was linear for hemorrhagic stroke, with increasing risk associated with increasing consumption, whereas there was a curvilinear relationship for ischemic stroke, with a protective effect of alcohol for low to moderate consumption and increased risk for higher exposure. Women who consumed 3 or more drinks on average/day had higher risk than men. 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. A meta-analysis including 35 observational studies examining the effects of alcohol consumption on stroke risk over a follow-up period of 4-30 years revealed a J-shaped relationship between the amounts of alcohol consumed per day and the risk of ischemic stroke (Reynolds et al. 2003). Individuals who consumed <12 grams of alcohol per day had the lowest risk for ischemic stroke (RR = 0.80, 95% CI 0.67-0.96), while those having more than 60 grams/day had the highest risk (RR = 1.69, 95% CI 1.34-2.15) when compared with a group of abstainers.

Birth Control/Hormone Replacement Therapy

Women taking oral contraceptive or hormone replacement therapy (HRT) may be at an increased risk of stroke. Bath & Gray (2005) conducted a meta-analysis including the results from 28 RCTs and found that HRT was associated with significant increases in the risk of total stroke (OR =1.29, 95% CI 1.13 to 1.47), non-fatal stroke (OR=1.23, 1.06 to 1.44), stroke leading to death or disability (OR=1.56, 1.11 to 2.20), and ischaemic stroke (OR=1.29, 1.06 to 1.56). They also reported that hormone replacement therapy was not associated with hemorrhagic stroke (OR=1.07, 0.65 to 1.75) or transient ischaemic attack (OR=1.02, 0.78 to 1.34). Similarly, Renoux et al. (2010) reported that, compared to non-users, women using oral hormone replacement therapy 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).
In terms of elevated risk of stroke associated with hormonal forms of birth control, the evidence is equivocal. 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. In a large cohort study of 49, 259 Swedish women aged 30-49, Yang et al. (2009) reported that the risk of fatal or nonfatal ischemic or hemorrhagic stroke was not significantly increased. The associations were not influenced by age at menarche nor with parity status.

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. Kaku & Lowenstein (1990) reported that the risk of stroke associated with (any) drug abuse was significantly higher compared with non-drug users (RR=06.5, 95% CI 3.1-13.6). There was a strong temporal relationship whereby the risk was highest during the first 6 hours after use and decreased over time. 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). The association between cannabis use and stroke does not appear to be as strong. While Barber et al. (2013) found no association between stroke and cannabis use (OR=1.59, 95% CI 0.71-3.70), Westover et al. (2007) reported that cannabis use was associated with an increased risk of ischemic stroke (OR=1.76, 95% CI 1.15-2.71) but not hemorrhagic stroke (OR=1.36, 95% CI 0.90-2.06), after adjusting for age, sex, ethnicity and current tobacco use.

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). There appears to be a dose-response relationship between increased cigarette smoking and stroke risk. In The Physician's Health Study (Robbins et al. 1994), the risk of non-fatal stroke was significantly higher among those currently smoking ≥20 cigarettes/day compared with those who never smoked. (RR=2.52, 95% CI 1.75 to 3.61). For those currently smoking <20 cigarettes/ day, the stroke risk remained elevated (RR=2.02, 95% CI 1.23 to 3.31). A recent systematic review & meta-analysis (Peters et al. 2013) that reported sex-specific risk of current smokers vs. non-smokers included 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). 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) was also associated with current smoking in Phase 1 of the case-control INTERSTROKE Study (O'Donnell et al. 2010). 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. Results from the Cardiovascular Health Study (Kaplan et al. 2005) including persons over the age of 65 years, indicated that smoking was associated with a significantly increased risk for stroke recurrence (HR= 2.06; 95% CI, 1.39–3.56).
Both pharmacological agents and behavioural intervention strategies have proved effective as smoking cessation interventions. A Cochrane review of reviews that examined the effectiveness of pharmacological treatments to promote smoking cessation in adults was 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 agonists. 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%.
Non-pharmacological and combination therapy have been shown to be effective in achieving sustained smoking cessation. A recent Cochrane Review authored by Stead & Lancaster (2012a) evaluated behavioral support with the addition of the availability of pharmacotherapy compared with a control condition receiving usual care or brief advice or less intensive behavioural support. The results from 41 RCTs including participants from both community and healthcare settings, most of whom smoked >20 cigarettes/day, were included. Most studies supplied nicotine replacement therapy (provided as patch or gum) while behavioural support was typically provided by specialists in cessation counselling, but was also provided by peer counsellors, trained nurses and usual care providers and took the forms of telephone, mail, individual and group sessions. Combination therapy was associated with the greatest chance of cessation of smoking at 6 months (RR=1.82, 95% CI 1.66-2.00, p< 0.0001). In studies that recruited participants from healthcare settings, the probability of success was greater (RR=2.06 vs. 1.53). There was no association between number of sessions provided and success of quitting (1-3 vs. 4-8 vs. >8) or the planned duration of contact (total minutes) (up to 30 vs. 31-90 vs. 91-300 vs. >300).
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.

Motivational interviewing, by itself has also shown to be an effective strategy to achieve sustained smoking cessation. Using the results from 14 RCTs, Lai et al (2010) examined the use of 1-4 sessions (15-45 minutes/session) of motivational interviewing (MI) compared with control groups who received brief advice, or routine care. Motivational interviewing was associated with a significantly increased probability of achieving long-term smoking cessation (RR 1.27, 95% CI 1.14- 1.42). Chances of success were greater when delivered by a general practitioner, compared with a nurse or counsellor. While both single compared and multiple sessions were both effective, sessions of >20 minutes duration were more effective compared with shorter sessions (RR= 1.31, 95% CI 1.16 to 1.49 vs. 1.14, 95% CI 0.80 to 1.16).
The use of electronic cigarettes (e-cigarettes) has increased in recent years, and remains controversial. They may be used as an alternative to conventional cigarettes or as an aid in smoking cessation programs. The current practice recommendations make no statements regarding their use. Although the use of e-cigarettes has been shown to significantly reduce the use of conventional cigarettes, in persons who wish to quit smoking (and in those with no desire to quit), data regarding their safety are limited.

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. Poor- or non-compliance to recommended medications may be due to several factors including inadequate or marginal health literacy, number of co-morbid conditions, adverse effects of treatment and cost (MacLaughlin et al. 2012). Non-compliance with diet regimens and other lifestyle factors is often a result of the interplay between patients' age, emotions, the reason they were given to control diet as well as their ability or desire to return for follow-up education (Travis 1997). Additional stroke-related factors, such as a lack of motivation, musculoskeletal issues, fatigue, and increasing age, may pose barriers to compliance with exercise programs or reduced leisure activities (Jurkiewicz et al. 2011). Therefore, early initiation of effective post stroke prevention strategies, maintained indefinitely with continuous monitoring by way of follow-up appointments, home visits or telephone check-in is essential. Bushnell et al. (2014) suggest a comprehensive model of stroke prevention, including the recognition of non-adherence, and understanding the factors associated with non-adherence. Moreover, clinician need to consider their patient demographic how they deliver secondary prevention treatment, with an emphasis on communication and education (Travis 1997, Hedegaard et al. 2015).

Lifestyle Management Evidence Tables and Reference List

3.0 Blood Pressure and Stroke Prevention

Secondary Prevention of Stroke **3. Blood Pressure and Stroke Prevention**

Update 2016

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

3.0 Hypertension is the single most important modifiable risk factor for stroke. Blood pressure should be assessed and managed in all persons at risk for stroke [Evidence Level A].

3.1 Blood pressure assessment

i. All persons at risk of stroke should have their blood pressure measured routinely, 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 Hypertension Canada Guidelines and Protocols for Blood Pressure Measurement (http://guidelines.hypertension.ca/).*

iii. Patients found to have elevated blood pressure (systolic greater than 130 mmHg and/or diastolic greater than 85 mmHg) should undergo thorough assessment for the diagnosis of hypertension [Evidence Level C].

   a. A specific follow-up visit may be scheduled and completed for the assessment and diagnosis of hypertension following an initial elevated blood pressure measurement [Evidence Level C].

   b. During a specific visit for assessment of hypertension consider including three blood pressure measurements conducted in accordance with the current g Hypertension Canada Guidelines [Evidence Level C]. *Refer to Hypertension Canada Algorythm for Diagnosis of Hypertension, Figure 3.1.*

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 counseling and lifestyle modificationinterventions [Evidence Level B]. *Refer to recommendations in Section 2 on Lifestyle Management for additional information.*

3.2 Blood pressure management

i. For patients **who have had a 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].

   a. For patients **who have had a small subcortical stroke,** blood pressure lowering treatment to achieve a systolic target of consistently lower than 130 mm Hg is reasonable [Evidence Level B] (New for 2017)

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

iii. **In patients with non-diabetic chronic kidney disease and stroke**, blood pressure lowering treatment is recommended for the prevention of first or recurrent stroke to attain a blood pressure consistently lower than 140/90mm Hg [Evidence Level C].

iv. Randomized controlled trials have not defined the optimal time to initiate blood pressure lowering therapy after 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).*

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

vi. For children, blood pressure lowering should be targeted to below the 95%ile on normative value tables for age, height and gender [Evidence Level B*]. http://www.statcan.gc.ca/pub/82-625-x/2012001/article/11713-eng.htm*

Clinical Considerations

i. Children who have had a stroke, and their families, should be counselled to avoid hypotensive situations where they might drop their cerebral perfusion pressure and risk ischemia, such as dehydration especially with vomiting/diarhrea,

Notes:

- *For recommendations on specific agents and sequence of agents for the secondary prevention of ischemic stroke, refer to the Canadian Hypertension Education Program treatment guidelines, and refer to Figure 3.2.*
- *Refer to Secondary Prevention of Stroke Section 2 for further recommendations on sodium reduction.*

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. A number of trials have shown a 28 percent risk reduction in recurrent stroke in patients treated with blood pressure lowering medication.

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.

System Implications

- 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.
- Stroke prevention, including routine blood pressure monitoring, offered by primary care providers in the community as part of comprehensive patient management.
- Increased availability and access to education programs about hypertension diagnosis and management for adults and children for healthcare providers across the continuum of care.
- 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.
- Universal access to cost-effectivepharmaceuticals, regardless of ability to pay or geograpy through private and/or public drug coverage plans which can help manage hypertension in addition to behavioural modification.

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

- 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.
- 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.
- 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.
- Prescriptions given to a patient do not imply compliance.
- 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

- Canadian Hypertension Education Program (CHEP) 2014 Recommendations: http://www.hypertension.ca/en/chep
- Canadian Task Force on Preventive Health Care for primary prevention screening guidelines for hypertension:http://canadiantaskforce.ca/ctfphc-guidelines/2012-hypertension/
- HSF Blood Pressure Management resources: http://www.heartandstroke.on.ca/site/c.pvI3IeNWJwE/b.9150999/k.9298/HMP_Resources.htm

Patient Information

- My Heart&Stroke Blood Pressure Action Plan: http://www.heartandstroke.ca/bp
- Canadian Hypertension Education Program: http://www.hypertension.ca/en/public
- DASH diet: http://www.heartandstroke.com/site/c.ikIQLcMWJtE/b.3862329/k.4F4/Healthy_living__The_DASH_Diet_to_lower_blood_pressure.htm
- High blood pressure information http://www.heartandstroke.on.ca/site/c.pvI3IeNWJwE/b.4010315/k.E295/Heart_Disease__Get_your_blood_pressure_under_control.htm
- Stroke medications: http://www.heartandstroke.com/site/c.ikIQLcMWJtE/b.3484223/k.71D9/Stroke___Medications.ht
- Hypertension Canada Patient Resources Including:
  Understanding and Managing Blood Pressure - an overview of what blood pressure is, and how to manage and control it
  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 2017

Hypertension Increases the Risk of Stroke

There is a well-established association between hypertension and increased risk of stroke. In fact, it is regarded as the most important modifiable risk factor. Results from Phases 1 and 2 of the INTERSTROKE study (O'Donnell et al. 2010, O'Donnell et al. 2016), a case-controlled study examining the contribution of specific risk factors to the burden of stroke across, indicated that five risk factors account for more than 80% of the risk for stroke. Among others, including current smoking, abdominal obesity, diet, and physical activity, hypertension was found to be the most significant. In phase 1 of the study, which included a sample size of 6,000, 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 included a larger sample size (n=26,919), and 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. Bestehorn et al. (2008) included the results from 47,394 patients diagnosed with hypertension who were under the care of 2,482 general physicians and reported an overall 10-year stroke rate of 26%. The risk increased to 50% with the addition of other co-morbidities. 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 TIA, 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

Description of many of the non-pharmacological approaches exist to reduce/manage blood pressure, including following a healthy diet, engaging in regular physical activity, consuming modest amounts of alcohol, reducing dietary sodium, avoiding tobacco exposure and managing high stress levels, are presented in other sections. The current recommendations to the pharmacological treatment of hypertension do not advise any particular dose/agent or combinations of agents to meet target blood pressures of <140/90 mg/Hg, (or <130/80 in persons with diabetes and kidney disease), while suggesting that angiotensin-converting enzyme (ACE) inhibitor/diuretic combination is preferred. While the Canadian Hypertension Education program (CHEP) suggests a more conservative systolic blood pressure target for the elderly (≥80 years, 150 mm Hg) due to their increased risk for falls, the present Canadian Best Practice Recommendations for Stroke Care does not differentiate based on age.

Numerous large, randomized controlled trials examining the effectiveness of a variety of antihypertensive agents, used alone, or in combination with other agents, have been published over the past 30 years. Many aimed to establish the superiority of one treatment regimen, or approach over another. These trials are characterized by large sample sizes, and are of high methodological quality. The Losartan Intervention For Endpoint reduction in hypertension (LIFE, Dahlof et al. 2002) and Study on Cognition and Prognosis in the Elderly (SCOPE, Lithell et al. 2003) studies demonstrated the efficacy of angiotensin receptor blockers (ARBs) for both primary and secondary prevention of stroke. Treatment with ARBs was superior to either placebo or atenolol-based antihypertensive regimen. The risk of cardiovascular mortality, stroke and myocardial infarction (combined) was reduced by 13% and 11%, respectively. The results of the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) trial (Jameson et al. 2008) suggested that a higher proportion of persons achieved adequate blood pressure control (defined as< 140/90 mm Hg), using a combination of benazepril–amlodipine compared with benazepril + hydrochlorothiazide (75.4% vs.72.4%). There were fewer cardiovascular events/deaths associated with the addition of amlodipine (HR= 0.80, 95% CI, 0.72 to 0.90, p<0.001), with non-significant reductions in the risk of death from cardiovascular causes between groups or fatal/nonfatal stroke. The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) compared: (1) ACE inhibitor ramipril; (2) the angiotensin-receptor blocker telmisartan; and (3), and the combination of the 2 drugs in patients who could not tolerate ACE inhibitors, among patients with vascular disease or high-risk diabetes (Yusef et al. 2008a). The researchers reported

that telmisartan was equivalent to ramipril in patients with vascular disease or high-risk diabetes, and was associated with less angioedema. The combination of the 2 drugs was associated with more adverse events without an increased benefit. In the Prevention Regimen For Effectively Avoiding Second Strokes (PRoFESS) Trial (Yusef et al. 2008b), the additional of telmisartan was not associated with a significant reduction in the risk of recurrent stroke within a median of 2.5 years follow up (HR=0.95, 95% CI 0.86 to 1.04, p= 0.23). Most recently, in the blood-pressure lowering arm of the Heart Outcomes Prevention Evaluation (HOPE) 3 trial (Lonn 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 candesartan + hydrochlorothiazide or placebo. Although blood pressures were significantly lower in the active treatment group at the end of follow-up (median of 5.6 years), the risks of the primary and secondary outcomes, as well as fatal and nonfatal stroke, were not reduced significantly. In sub group analysis, patients in the highest blood pressure group benefited from active treatment. In the statin + blood pressure lowering arm of the HOPE-3 trail (Yusuf et al. 2016), the addition of rosuvastatin to the combination antihypertensive agents did result in a significantly reduced risk of cardiovascular events, including fatal or nonfatal stroke (HR=0.56, 95% CI 0.36-0.87).

The Secondary Prevention of Small Subcortical Strokes (SPS3 Trial) examined the effectiveness of medical management to reduce recurrent stroke. 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). In the Systolic Blood Pressure Intervention Trial (SPRINT), the potential benefit of a more aggressive blood pressure target was examined (Wright et al. 2015) among patients who were at increased risk of cardiovascular disease, without a history of diabetes. Persons with a history of previous stroke were excluded. Patients with an increased SBP (>130-180 mm Hg) were randomized to receive intensive treatment with a goal of SBP <120 mm Hg using 2-drug therapy, if required or standard treatment with a goal of SBP <140 mm Hg, for up to 6 years. The study was terminated early when the superiority of intensive therapy was demonstrated during interim analysis. The risk of the primary outcome (first occurrence of myocardial infarction, acute coronary syndrome, heart failure or cardiovascular death) was significantly lower for patients in the intensive group (HR=0.75, 95% CI 0.64-0.89, p<0.001); however, the risk of stroke was not (HR=0.89, 95% CI 0.63-1.25, p=0.50). The risks of serious adverse events including episodes of hypotension, syncope, electrolyte abnormality, and acute renal failure were all significantly higher in the intensive group. The potential benefit of achieving a lower diastolic BP was examined in the Hypertension Optimal Treatment (HOT) Trial (Hanssen et al. 1998). This trial included 18,790 patients, aged 50 to 80 years with DBP between 100 mm Hg and 115 mm Hg, of who a small number of participants (~1.2%) had experienced a previous stroke. Participants were randomly allocated to receive antihypertensive treatment to achieve diastolic BP targets of ≤ 90 m Hg, ≤ 85 mm Hg or ≤ 80 mm Hg, using a 5-step treatment program. There were no differences among groups for the risks of major cardiovascular events, all stroke or total mortality. Among the 1,501 participants with diabetes at baseline, the risk of major cardiovascular events was significantly increased in the highest target blood pressure group, compared with the lowest (RR=2.06, 95% CI 1.24-3.44), but without an increase in stroke risk (RR=1.43, 95% CI 0.68-2.99).

Studies examining the benefits versus risks of hypertension management in the very elderly (≥80 years) have emerged in the past few years. In the Hypertension in the Very Elderly Trial (HYVET), elderly patients were randomly assigned to receive either antihypertensive therapy, using indapamide as a first-line agent or matching placebo. Lowering mean blood pressure by 15.0/6.1 mm Hg was associated with a 30% reduction in the rate of fatal or nonfatal stroke (95% CI –1% to 51%, p = 0.06), a 39% reduction in the rate of death from stroke (95% CI 1% to 62%, p = 0.05), a 21% reduction in the rate of death from all

causes (95% CI 4% to 35%, *p* = 0.02), and a 23% reduction in the rate of death from cardiovascular causes (95% CI –1% to 40%, *p* = 0.06) over a (median) follow-up period of 1.8 years (Beckett et al. 2008). The authors concluded that antihypertensive treatment in patients 80 years of age or older was beneficial. The open-label active treatment extension of the HYVET study included 1682 patients in both arms of the trial (Beckett et al 2012) with same target blood pressure levels <150/80 mm Hg. While there were no significant between-group differences in the incidence of fatal/nonfatal stroke, heart failure, or all cardiovascular events (12 vs. 13, HR= 0.78, 95% CI 0.36 to 1.72, p=0.55), the risks of all-cause mortality and cardiovascular mortality were significantly lower in patients previously receiving active treatment. There was a significant reduction in the risk of fatal/nonfatal stroke and stroke mortality associated with active treatment in the per-protocol analysis (HR=0.63, 95% CI 0.44-0.92, p<0.016 and HR=0.55, 95% CI 0.33-0.92, p<0.021, respectively) (Reisin et al. 2014).

The evidence for the beneficial effect of pharmacological treatment for hypertension in reducing stroke risk and mortality from stroke is strengthen from the results of several meta-analyses. 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 mmHg) with usual control (SBP 130 to 139 mmHg) 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. Law et al (2009) included the results of 147 RCTs (n=464,000) comparing: i) blood pressure lowering medications vs. placebo or usual care; and ii) trials compared different types of blood pressure medications. A blood pressure treatment-associated reduction of 10 mm Hg systolic and 5 mm Hg diastolic was associated with a reduced risk of stroke (RR=0.59, 95% CI 0.52-0.67). The risk of stroke was significantly reduced in trials that included persons with no prior history of stroke, a history of CHD, and a history of stroke. A Cochrane meta-analysis authored by Musini et al. (2009) included 15 trials, (24,055 subjects ≥ 60 years) with moderate to severe hypertension who were treated primarily with first-line thiazide diuretic therapy for a mean duration of treatment of 4.5 years. Treatment was associated with reduced total mortality, (RR= 0.90, 95% CI 0.84-0.97), and reduced total cardiovascular morbidity and mortality (RR=0.72, 95% CI 0.68-0.77). In the three trials restricted to persons with isolated systolic hypertension, the benefit was similar. In very elderly patients, ≥ 80 years the reduction in total cardiovascular mortality and morbidity was similar; however, there was no reduction in total mortality, (RR=1.01, 95% CI 0.90, 1.13). Withdrawals due to adverse effects were increased with treatment (RR= 1.71, 95% CI 1.45, 2.00).

Blood Pressure and Stroke Prevention Evidence Tables and Reference List

Figure 3.1: CHEP Blood Pressure Measurement Algorithm

(Reproduced with Permission, CHEP 2016)

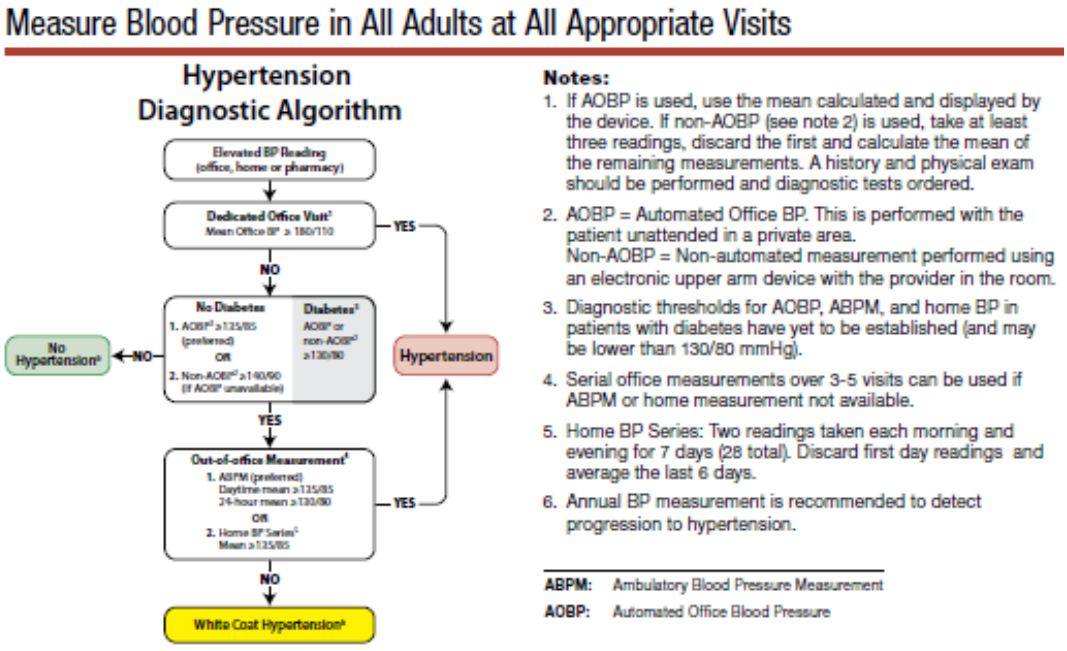
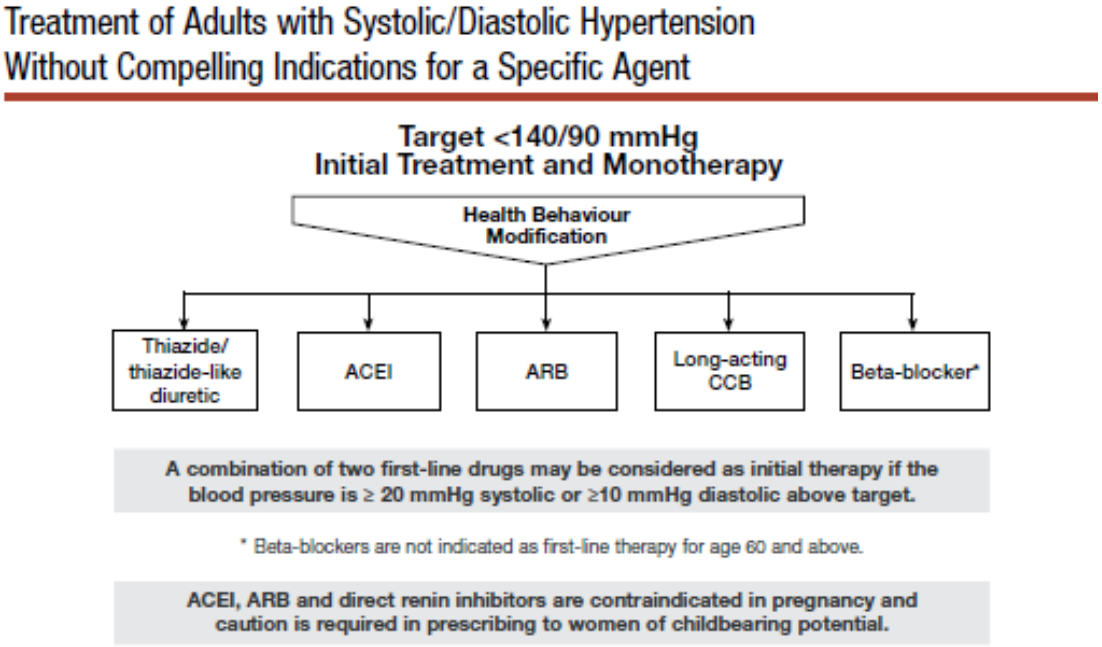


Figure 3.2: CHEP Treatment Algorithm 2016

(Reproduced with Permission, CHEP 2016)



4.0 Lipid Management

Secondary Prevention of Stroke **4. Lipid Management**

Update 2017

4.0 Patients who have had an ischemic stroke or transient ischemic attack should have their serum lipid levels assessed and aggressively managed [Evidence level A].

4.1 Lipid assessment

i. Lipid levels, including total cholesterol, total triglycerides, low-density lipoprotein [LDL] cholesterol, and high-density lipoprotein [HDL] cholesterol, should be measured on all patients presenting with stroke or TIA [Evidence Level B].

*Note: For diagnosis and management of dyslipidemia in the **primary prevention** of cardiovascular events, including stroke, refer to the current Canadian Cardiovascular Society Dyslipidemia clinical practice guidelines August 2016 CJC.*

4.2 Lipid management

i. Patients with ischemic stroke or transient ischemic attack should be managed with aggressive therapeutic lifestyle changes to lower lipid levels, including dietary modification, as part of a comprehensive approach to lower risk of first or recurrent stroke unless contra-indicated[Evidence Level B]. *Refer to Prevention of Stroke Module, Section 2 for Lifestyle Management recommendations.*

ii. A statin should be prescribed as secondary prevention to patients who have had an ischemic stroke or transient ischemic attack in order to achieve a target LDL cholesterol consistently less than 2.0 mmol/L or >50% reduction of LDLcholesterol, from baseline [Evidence Level B]. (Ref: CCS Lipid Guideline update 2016)

   a. For individuals with stroke, a recent acute coronary syndrome or established coronary disease, treatment to more aggressive targets (LDL-C <1.8 mmol/L or >50% reduction) should be considered [Evidence Level A].

iii. Adults with diabetes and ischemic stroke are at high risk of further vascular events and should also be treated with a statin to achieve a low-density lipoprotein cholesterol ≤2.0 mmol/L [Evidence Level B].

iv. Statin therapy is not indicated for prevention of intracerebral hemorrhage [Evidence Level B].

Refer to the Canadian Cardiovascular Society 2016 Guidelines for the Diagnosis and Treatment of Dyslipidemia for additional information.

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 20 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 the childhood obesity epidemic, dyslipidemia is becoming a growing issue in paediatric stroke cases; therefore, fasting lipid panels should be part of the assessment of paediatric stroke cases.

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

- 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.
- Stroke prevention, including lipid level monitoring offered by primary care providers in the community as part of comprehensive patient management.
- Increased availability and access to education programs on dyslipidemia diagnosis and management for healthcare providers across the continuum of care.
- Continued alignment with recommendations and guidelines developed by the Canadian Cardiovascular Society Dyslipidemia group.
- Universal access to cost-effective pharmaceuticals, regardless of ability to pay or geograpy through private and/or public drug coverage plans which can help manage risk factors in addition to behavioural modification.

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

- Performance measures 1 and 2: Data may be available through the Canadian Community Health Survey.
- Performance measure 2: Blood values should be taken from official laboratory reports where possible
- Performance measure 3: Data sources may include physician order sheets, physicians' and nurses' notes, discharge summaries, or copies of prescriptions given to patients.
- 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.
- Prescriptions given to a patient do not imply compliance.

Implementation Resources and Knowledge Transfer Tools

Health Care Provider Information

- Canadian Cardiovascular Society Dyslipidemia Recommendations: http://www.onlinecjc.ca/article/S0828-282X(16)30732-2/abstract
- Framingham Cardiovascular Risk Calculator: http://www.framinghamheartstudy.org/risk-functions/index.php
- National Heart, Lung and Blood Institute Patient Educational Materials:

- https://www.nhlbi.nih.gov/health-pro/resources

Patient Information

- Getting your cholesterol in check: http://www.heartandstroke.com/site/c.ikIQLcMWJtE/b.3484027/k.8419/Heart_disease__High_blood_cholesterol.htm
- Food sources of cholesterol: http://www.dietitians.ca/Nutrition-Resources-A-Z/Factsheets/Fats/Food-Sources-of-Cholesterol.aspx
- Strokemedications: http://www.heartandstroke.com/site/c.ikIQLcMWJtE/b.3484223/k.71D9/Stroke___Medications.htm
- Cholesterol Levels Calculator: http://bodyandhealth.canada.com/health_tools.asp?t=12&text_id=2751&channel_id=10&relation_id=10864
- College of Family Physicians of Canada: http://www.cfpc.ca/ProjectAssets/Templates/Resource.aspx?id=1364
- AHA resources: http://www.heart.org/HEARTORG/Conditions/Cholesterol/CholesterolToolsResources/Cholesterol-Tools-and-Resources_UCM_001216_Article.jsp

Summary of the Evidence 2017

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. Guidelines differ with respect to their global approach to treatment, with some suggesting a treat to target approach (e.g. 2016 Canadian Cardiovascular Society Guidelines), a lifetime risk, or lowest is best approach, while others make no recommendations for or against specific LDL-C or non–HDL-C targets for either primary or secondary prevention of atherosclerotic cardiovascular disease (ASCVD), while recommending that high-intensity statin therapy should be used in persons with ASCVD or significant elevations in LDL-C (e.g. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Risk in Adults).

Evidence from several systematic reviews have demonstrated a significant reduction in overall risk of ischemic stroke associated with lipid-lowering therapies. Patients with a history of stroke or transient ischemic attack, or who have a markedly higher baseline risk of recurrent cerebrovascular events, may experience greater benefit. The Cholesterol Treatment Trialists (Baigent et al. 2010) included 26 RCTS in which the treatment aim was solely the reduction of LDL cholesterol. Overall, a 1 mmol/L reduction in LDL-chol was associated with a significant reduction in the risk of any major vascular event (RR=0.78, 95% CI 0.76-0.80, p<0.0001), but was not associated with reductions in stroke mortality (RR=0.96, 95% CI 0.84-1.09). In a more recent CTT publication that included the results from 27 RCTs, the benefits of therapy between men and women were compared. Overall, statins reduced the risk of major vascular events by 21% per each 1.0 mmol/L reduction in LDL-chol (RR=0.79, 95% CI 0.77-0.81, p<0.0001), with no significant interaction reported for sex. Similarly, for the outcome of stroke, the risk was significantly reduced with statin therapy (RR=0.85, 95% CI 0.80-0.89, p<0.00001), with no significant differences by sex. In another CTT analysis (Mihaylova et al. 2012) patients were classified into one of 5 groups, based on 5-year risk of major vascular events from <5% to ≥30%. There was a significant reduction in the risk of major vascular events in all risk groups in patients with and without a previous history of vascular disease. For the outcome of stroke, except for the lowest risk group, lipid-lowering treatment was associated with a

significantly reduced risk of stroke. Other meta-analyses have also demonstrated a reduction in stroke risk associated with statin therapy. O'Regan et al. (2008) evaluated statin therapy for all stroke prevention, using the results from 42 trials (n = 121,285). The risk of all-cause mortality associated with statin treatment was significantly reduced (RR=0.88, 95% CI 0.83-0.93) as was the risk of all strokes (RR=0.84, 95% CI 0.79-0.91). In meta-regression, LDL-chol was the only predictor of effect size, whereby each unit increase in serum cholesterol was associated with a 0.3% increase in mortality risk (RR=1.003, 95% CI 1.005-1.006, p=0.02). Statin treatment was associated with a reduction in cardiovascular death and ischemic stroke, but not hemorrhagic or fatal stroke.

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 apoproteinB-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). 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 cardiovascular 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. Higher doses of statins have been associated with greater protection. In the Treating to New Targets (TNT) Trial, 10,001 participants, with clinically evident coronary heart disease and LDL-chol of <3.4 mmol/L were randomized to receive 80 vs. 10 mg/day of atorvastatin for approximately 5 years. LDL chol levels were reduced from 2.6 to 2.0 mmol/L (80 mg group), but were unchanged in the 10 mg group. Fewer persons in the 80 mg group experienced a fatal/non-fatal stroke or TIA (HR=0.77, 95% CI 0.64-0.93, p=0.007). In the Study of the Effectiveness of additional Reductions in Cholesterol & Homocysteine (SEARCH) Collaborative Group Study (Armitage et al. 2010), participants were randomized to receive 20 vs. 80 mg simvastatin for almost 7 years. The reduction in the risk of stroke associated with 80 mg simvastatin was significantly lower for the outcome of any stroke (RR=0.91, 95% CI 0.77-1.08, p=0.03),

although cases of definite myopathy were higher.

There has only been one large RCT evaluating statin therapy 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 TIA 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). Post hoc analysis in the SPARCL trial found the following characteristics to be independent predictors to increased risk of hemorrhagic stroke: atorvastatin treatment, history of hemorrhage stroke, male gender, increased age, and Stage II hypertension (SBP > 160 mmHg or DBP > 100 mmHg.) (Goldstein et al. 2008). A small retrospective study including 215 persons aged 15 to 49 years with first-ever ischemic stroke of unknown etiology explored the relationship between subsequent stroke and statin use (Putaala et al. 2011). Compared with patients who had been continuous users of statins, after a mean of 9 years' follow-up, statin therapy (continuous and non-continuous) was associated with a significant reduction in the occurrence of stroke, myocardial infarction and other vascular events (HR=0.23, 95% CI 0.08-0.66, p=0.006).

Evolocumab is an example of a monoclonal antibody that inhibits proprotein convertase subtilisin–kexin Type 9 (PCSK9), and reduces low-density lipoprotein (LDL) C. While no recommendations have been made regarding the addition of specific agents to standard statin treatment in this update of the Canadian Best Practice Recommendations, the results from a recent large RCT suggests its potential clinical application. 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 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). 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).

Lipid Management Evidence Tables and Reference List

CCS 2016 Lipid Guidelines

(Anderson et al; Canadian Journal of Cardiology 32 (2016) 1263-1282)

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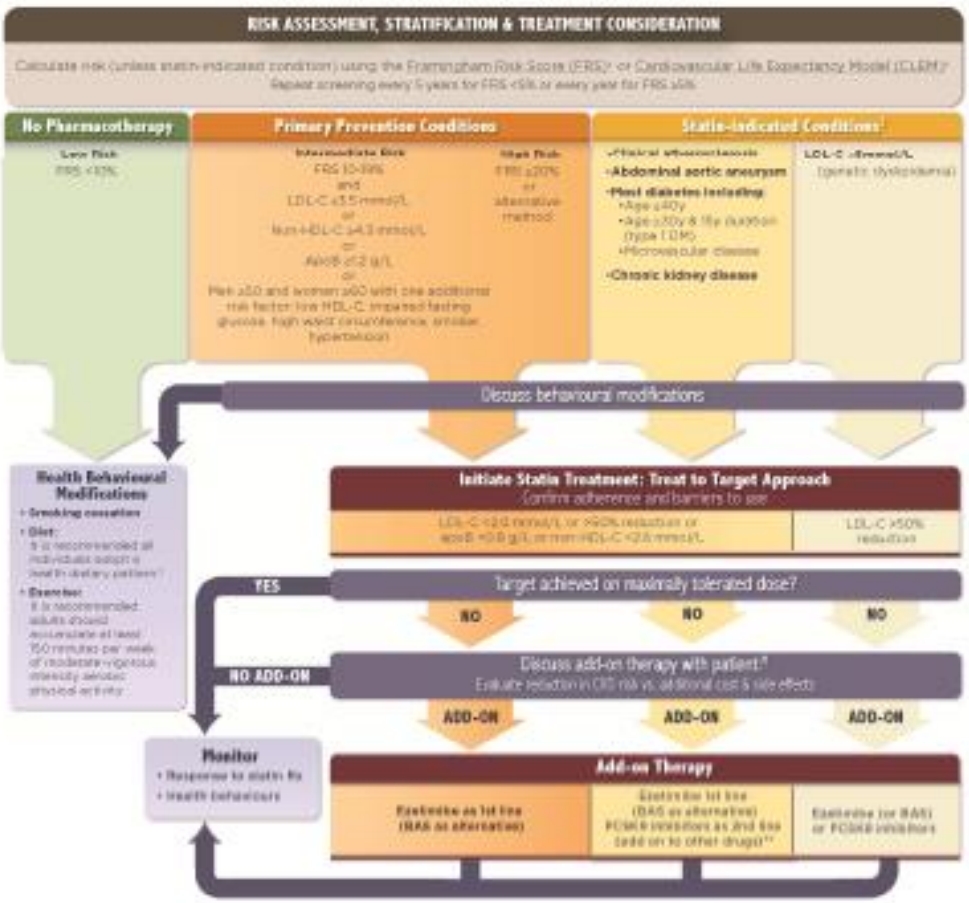
http://www.onlinecjc.ca/article/S0828-282X(16)30732-2/pdf



5.0 Diabetes and Stroke

Secondary Prevention of Stroke **5. Diabetes and Stroke**

Update 2017

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

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 (TIA) 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 inpatient or outpatient setting [Evidence Level C; Diabetes Canada 2016].

ii. For patients with diabetes and either ischemic stroke or transient ischemic attack, glycated hemoglobin (A1C) should be measured 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: however, lowering A1C values to ≤7% in both type 1 and type 2 diabetes (and stroke or transient ischemic attack), provides strong benefits for the prevention of microvascular complications [Evidence Level A].

ii. 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 preprandial plasma glucose target of 4.0 to 7.0 mmol/L [Evidence Level B].

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

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

Clinical Consideration(New 2017):

i. The results from a recent trial, *Pioglitazone after Ischemic Stroke or Transient Ischemic Attack* (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. The decision to use this agent could be considered based on the specific risk profile for each patient.

ii. More intensive glucose control (A1C ≤6.5%), may be considered in patients with a shorter duration of diabetes, no evidence of significant cardiovascular disease and longer life expectancy, provided this does not result in a significant increase in hypoglycemia (CDA 2016).

Refer to the Diabetes Canada 2013 Clinical Practice Guidelines and CDA 2016 Interim Update for additional information.

Rationale

Diabetes is a major risk factor for cardiovascular disease and is recognized as an independent risk factor for ischemic stroke. 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.

System Implications

- 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.
- Coordinated education and support programs for persons with diabetes to increase compliance and reduce ongoing risks for cardiovascular complications.
- Increased availability and access to education programs for healthcare providers across the continuum of care on management of patients with diabetes and stroke
- Continued alignment with recommendations and guidelines developed by Diabetes Canada
- Universal access to cost-effective pharmaceuticals, regardless of ability to pay or geograpy through private and/or public drug coverage plans which can help manage risk factors in addition to behavioural modification.

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

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

Implementation Resources and Knowledge Transfer Tools

Health Care Provider Information

- Diabetes Canada Clinical Practice Guidelines: http://guidelines.diabetes.ca/?_ga=1.128071051.68732641.1457965214
- Diabetes Canada professional resources: http://guidelines.diabetes.ca/healthcareprovidertools

Patient Information

- Diabetes Canada http://www.diabetes.ca/
- Diabetes Canada patient resources: http://guidelines.diabetes.ca/PatientResources.aspx
- Multicultural resources: http://www.diabetes.ca/diabetes-and-you/healthy-living-resources/multicultural-resources

Summary of the Evidence 2017

In persons with diabetes, the risk of stroke is increased, with a higher risk of ischemic, rather than hemorrhagic stroke. 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 persons 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 from 8.1% at baseline 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 hypoglycaemia 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. Empagliflozin is an example of a selective inhibitor of sodium glucose cotransporter (SGLT-2) that has been demonstrated to reduce glycated hemoglobin levels and improve cardiovascular outcomes. A recent large RCT included 7,020 adults with type 2 diabetes, an estimated glomerular filtration rate of ≥30mL/min and established cardiovascular disease (Zinman et al. 2015). In this trial, the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME), patients were randomized to receive 10 mg or 25 mg of empagliflozin, or placebo once daily for the duration of the trial. Background glucose-lowering therapy was also used, as required. After a median of 3.1 years follow-up, the risk of the primary outcome, which was a composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke, was significantly reduced in the empagliflozin group (10.5% vs. 12.1%: HR=0.86; 95.02% CI 0.74- 0.99; p<0.001 for noninferiority; p=0.04 for superiority, both dose levels combined), but was not associated with a significantly reduced risk of fatal or nonfatal stroke. Although no recommendations have been made in the current Best Practices Update, the glucagon-like peptide 1 receptor, liraglutide, is another example of an agent that may be added to standard regimes. In the LEADER trial, (Marso et al 2016), 16% of patients had sustained a previous stroke. Patients in the intervention arm of the trial received 1.8 mg liraglutide daily for a median duration of 3.8 years. The risk of the primary outcome (death from cardiovascular causes, nonfatal MI, or nonfatal stroke) was significantly lower in the liraglutide group (HR=0.87, 95% CI 0.78–0.97, p=0.01 for superiority). The NNT to prevent one case of the primary outcome over 3 years was 66.

Lower blood pressure targets (<130/80 mm Hg) have been recommended for persons with diabetes by several organizations, including the most recent guidelines published by Hypertension Canada's 2016 Canadian Hypertension Education Program Guidelines for Blood Pressure Measurement, Diagnosis, Assessment of Risk, Prevention, and Treatment of Hypertension. A Cochrane review (Arguedas et al. 2013) included the results from 5 RCTs that compared 'lower' blood pressure targets (any target <130/85mmHg) with 'standard' targets (<140-160/90-100 mmHg). Participants were adults with type 2 diabetes and elevated blood pressure, or already receiving treatment for elevated blood pressure. In the single trial 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 n 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).

The Treating to New Targets study (Shepherd et al. 2006) demonstrated that intensive lipid-lowering

therapy with atorvastatin 80 mg/day provided significant clinical benefit beyond atorvastatin 10 mg/day in patients with patients with stable coronary artery disease and diabetes and LDL cholesterol levels of < 3.36 mmol/L. High-dose statin therapy was associated with a 25% reduction in major cardiovascular events. After a median follow-up period of 4.9 years, the primary end point (time to first major cardiovascular event), occurred less frequently in the high-dose group (17.9% vs. 13.8%, HR= 0.75, 95% CI 0.58–0.97; *p* = 0.026). Significant differences between the groups in favour of atorvastatin 80 mg were also observed for time to cerebrovascular event (HR 0.69, 95% CI 0.48–0.98; *p* = 0.037) and time to any cardiovascular event (HR 0.85, 95% CI 0.73–1.00; *p* = 0.044). There were no significant differences between the treatment groups in the rates of treatment-related adverse events or persistent elevations in liver enzymes.

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 in Ischemic Stroke and TIA

Secondary Prevention of Stroke 6. Antiplatelet Therapy in Ischemic Stroke and TIA

Update 2017

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

6.1 All patients with ischemic stroke or transient ischemic attack should be prescribed antiplatelet therapy for secondary prevention of recurrent stroke unless there is an indication for anticoagulation [Evidence Level A].

i. Acetylsalicylic acid (80 mg – 325 mg), combined acetylsalicylic acid (25 mg) and extended-release dipyridamole (200 mg), or clopidogrel (75 mg) are all appropriate options and selection should depend on the clinical circumstances [Evidence Level A].

a. Short-term concurrent use of acetylsalicylic acid and clopidogrel (up to 21 days) has not shown an increased risk of bleeding and may be protective following minor stroke or transient ischemic attack [Evidence Level B];

b. Longer-term use of acetylsalicylic acid and clopidogrel is not recommended for secondary stroke prevention, unless there is an alternate indication (e.g., coronary drug-eluting stent requiring dual antiplatelet therapy), due to an increased risk of bleeding and mortality [Evidence Level A]. *This combination of efficacy is currently being investigated in the POINT trial (www.Clinicaltrials.gov; Identifier NCT00991029).*

6.2 Paediatric Stroke Considerations:

i. In children with stroke the usual maintenance dosage of acetylsalicylic acid is 3 to 5 mg/kg per day for the prevention of recurrent stroke [Evidence Level B]. The usual maximum dose in adolescents is 81 mg/day.

a. There is no evidence available on the optimal duration of therapy; this should be based on individual clinical circumstances.

ii. The evidence for clopidogrel use in children is sparse at this time. Clopidogrel may be considered as an alternative for adolescents at a dose of 1 mg/kg/day up to a maximum of 75 mg/day especially in the context of ASA allergy. Younger children may have higher anti-platelet effects of clopidogrel, and the suggested doses should be considered within the range of 0.2 – 0.5 mg/kg/day [Evidence Level C].

Clinical Considerations: (New for 2017)

i. At the present time, there is not enough evidence to guide management if a patient has a stroke while on a specific antiplatelet agent. In all cases of recurrent stroke while on antiplatelet therapy, all other vascular risk factors and stroke etiology should be reassessed and aggressively managed.

ii. Expert opinion suggests that if a patient experiences a stroke while on ASA, it may be reasonable to consider switching to clopidogrel; if a patient experiences a stroke while on clopidogrel it may be reasonable to consider switching to combined acetylsalicylic acid (25 mg) and extended-release dipyridamole (200 mg).

Refer to Prevention of Stroke Section 7 on Stroke and Atrial Fibrillation for additional recommendations on anticoagulant therapy.

Rationale

Antiplatelet agents are considered a fundamental component of secondary stroke prevention. Several clinical trials have shown that antiplatelet medications (such asacetylsalicylic 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.

System Implications

- 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).
- Optimization of comprehensive stroke strategies at the local, regional and provincial levels to prevent the recurrence of stroke.
- 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 TIA 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

- Data sources include patient chart, nurses' notes, physicians' orders and discharge summary note. Documentation quality may affect ability to accurately monitor this performance measure.
- It may be a challenge to measure compliance and prescribing patterns in primary care.
- 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).
- 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

- Canadian Cardiovascular Society Antiplatelet Therapy Guidelines: http://www.onlinecjc.ca/article/S0828-282X%2813%2900443-1/abstract
- CHEST Antithrombotic Guidelines: http://www.chestnet.org/Guidelines-and-Resources/Guidelines-and-Consensus-Statements/Antithrombotic-Guidelines-9th-Ed
- Canadian Cardiovascular Society Antiplatelet Therapy Guidelines apps, pocket guides, slide decks and e-learning: http://www.ccsguidelineprograms.ca/index.php?option=com_content&view=article&id=141&Itemid=82
- Thrombosis Canada clinical guides: http://thrombosiscanada.ca/?page_id=18
- Praxbind checklist link


Idarucizamab checklist.docx


ANTIPLATELET DRUG COMPARISON CHART

- http://www.vhpharmsci.com/vhformulary/Tools/ANTIPLATELET%20DRUG%20COMPARISON%20CHART.pdf

Patient Information

- Antiplatelets: http://www.heartandstroke.com/site/c.ikIQLcMWJtE/b.3484139/k.C87F/Heart_disease__Antiplatelets.htm
- Thrombosis Canada clinical guides: http://thrombosiscanada.ca/?page_id=18 JD

Summary of the Evidence 2017

Substantial evidence from randomized trials and meta-analyses supports the use of antithrombotic agents in patients who have experienced an ischemic stroke or TIA 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

A meta-analysis conducted by The Antithrombotic Trialists' Collaboration (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 aspirin monotherapy was examined in patients who had experienced a previous stroke or TIA. In these trials, fewer patients receiving aspirin therapy experienced a vascular event (8.2% vs. 9.1%) representing an 11% odds reduction. In 65 trials examining aspirin monotherapy across doses ranging from <75mg to 1.500 mg, the mean percentage odds reduction of any vascular event was 23%. ASA and other forms of antiplatelet drugs reduced the incidence of nonfatal stroke by one-quarter. The Antithrombotic Trialists' Collaborative (ATTC) included the results of 18 RCTs examining aspirin therapy for primary (n=6 with 95,456 subjects) and secondary (n=16) prevention of vascular events (Baigent et al. 2009). In the primary prevention trials, there was a significant reduction in risk of any serious vascular event, but no significant reduction in the risk of stroke (RR=0.95, 95% CI 0.85-1.06, p=0.40), fatal stroke (RR=1.21, 95% CI 0.84-1.74) or nonfatal stroke (RR=0.92, 95% CI 0.79-1.07). Secondary prevention trials were associated with a reduced risk of stroke of unknown cause (RR=0.77, 95% CI 0.62-0.96), but no reduction in the risk of ischemic stroke (RR=0.78, 95% CI 0.57-1.06) or fatal stroke (RR=1.08, 95% CI 0.73-1.62).

Ticagrelor

While aspirin at varying doses is the most widely-used antiplatelet agent, the risk of hemorrhagic events, particularly gastrointestinal bleeding, remains substantial. The use of another agent, ticagrelor, a P2Y12 receptor inhibitor, has recently been studied as a potentially safer alternative to aspirin. In the Acute Stroke or Transient Ischemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes (SOCRATES) trial (Johnston et al. 2016), 13,199 patients who had experienced a minor stroke or high-risk TIA within the previous 24 hours were randomized to receive either ticagrelor or aspirin. At the end of

90 days, there were no significant differences between groups on the primary, secondary or safety outcomes between groups, indicating that ticagrelor was not superior to aspirin.

Dual vs. Monotherapy with Clopidogrel

Several large clinical trials have examined the combination of clopidogrel + aspirin vs. aspirin alone. While the results from some of these trials failed to demonstrate a significant further reduction in risk of recurrent stroke associated with dual therapy among patients who had already sustained a minor stroke or TIA, most reported an increased risk of bleeding events. The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial randomly assigned 15,603 patients with clinically evident cardiovascular disease or multiple risk factors to receive clopidogrel (75 mg/day) plus low-dose ASA (75 to 162 mg/day) or placebo plus low-dose ASA, with a median follow-up of 28 months (Bhatt et al. 2006). There was a non-significant reduction in the risk of the primary outcome (a composite of nonfatal stroke, nonfatal myocardial infarction or vascular death) associated with dual therapy (6.8% vs. 7.3%, RR=0.93, 95% CI 0.83-1.05, p=0.22). There were also non-significant reductions in death from any cause, death from cardiovascular causes and non-fatal MI associated with dual therapy. There was a significant reduction in the risk of all nonfatal stroke (1.9% vs. 2.4%, RR=0.79, 95% CI 0.64-0.98, p=0.03), but not nonfatal ischemic stroke (1.7% vs. 2.1%, RR=0.81, RR=0.64-1.02, p=0.07). More patients in the dual therapy group experienced moderate bleeding (2.1% vs. 1.3%, p<0.001) but there was no difference between groups in other adverse events (severe and fatal bleeding and ICH). The investigators concluded that, clopidogrel plus ASA was not significantly more effective than ASA alone in reducing the rate of myocardial infarction, stroke or vascular death. Similar results were reported in the Fast Assessment of Stroke and TIA to prevent Stroke Recurrence (FASTER) trial (Kennedy et al. 2007) where there was a non-significant reduction in the risk of stroke associated with clopidogrel use (7.1% vs. 10.8%, RR=0.7, 95% CI 0.3-1.2, p=0.19) and a significant 3% increase in risk (p=0.03) for symptomatic bleeding events in the groups allocated to clopidogrel. In the Secondary Prevention of Small Subcortical Strokes (SPS3) trial, patients were randomized to receive 325 mg of enteric coated aspirin + 75 mg clopidogrel daily or aspirin + placebo (Benavente et al. 2012). After a mean follow-up period of 3.4 years, the addition of clopidogrel was not associated with reductions in stroke, MI or death from vascular causes, but it was associated with an increased risk of all-cause mortality. A subgroup analysis that included patients who were on aspirin therapy at the time of the qualifying stroke demonstrated that the addition of 75 mg clopidogrel was not associated with reductions in the risk of stroke or MI, but was associated with a significant increase in death from any cause and vascular death (Cote et al. 2014). One recent major trial that did report a benefit of the addition of clopidogrel was the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial, in which investigators randomized 5,170 patients with minor ischemic stroke within 24 hours or high-risk TIA 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, p<0.001) or an MI, stroke or vascular death stroke (8.4% vs. 11.9%, HR=0.69, 95% CI 0.58- 0.82, p<0.001). There was no difference in (any) bleeding events between groups (2.3% vs. 1.6%, p=0.09). A recently published meta-analysis included the results from 13 RCTs (Palacio et al. 2015). Overall, the use of clopidogrel+ aspirin was associated with significantly reduced odds of any stroke (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), while the odds of major hemorrhage were not significantly increased (OR=0.91, 95% CI 0.40-2.07).

A single, large trial has examined the treatment contrast of clopidogrel + aspirin vs. clopidogrel alone (Deiner et al. 2004). The Management of Atherothrombosis with Clopidogrel in High-risk patients with recent TIA or ischemic stroke (MATCH) trial included 7,599 high-risk patients with recent ischemic stroke or transient ischemic attack and at least one additional vascular risk factor. All patients received 75 mg of clopidogrel daily; In addition, patients were randomized to receive 75 mg aspirin daily or placebo, daily for 18 months. The addition of aspirin did not reduce the occurrence of the primary outcome (a composite of ischemic stroke, myocardial infarction, vascular death or rehospitalization for acute ischemia:16% vs. 17%, Absolute Risk Reduction=6.4%, 95% CI -4.6%-16.3%, p=0.244), or the incidence of fatal/nonfatal stroke and vascular death (11% vs. 11%, ARR=0.75%, 95% CI -0.7%-2.2%, p=0.324) or any stroke (9% vs. 9%, ARR=0.20%, 95% CI -1.1%-1.55, p=0.79). The investigators concluded that the addition of ASA was associated with a nonsignificant reduction in major vascular events and a significant increase in the risk of life-threatening or major bleeding.

The use of clopidogrel among children for the prevention of stroke recurrence has not been well-studied. Soman et al. (2006) followed 17 children, aged 1 month to 17 years, for up to 4 years after arterial ischemic stroke. Children were started on clopidogrel after demonstrating failure or intolerance to aspirin. There were no cases of stroke recurrence during a mean follow-up of 1.8 years. No patient receiving monotherapy with clopidogrel reported any major complications, while two patients reported minor complications (hand numbness and headache) that were not thought to be medication related. Among 9 patients who received aspirin in addition to clopidogrel, there were 2 cases of intracranial bleeding.

Dual vs. Monotherapy with Dipyridamole

Dipyridamole is another antiplatelet agent that can be combined with aspirin for the prevention of stroke. The European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT) randomized 2,763 patients who had experienced a TIA or minor stroke within the previous 6 months to receive extended-release dipyridamole (200 mg bid) + aspirin (30 to 325 mg/d-mean dose, 75 mg, n=1,363) or aspirin (as above) alone for 3.5 years. Significantly fewer patients in the dual therapy group experienced the primary outcome (composite of vascular death, nonfatal stroke, nonfatal MI or major bleeding complication: 12.7% vs. 15.7%, HR=0.80, 95% CI 0.66-0.98, NNT=104), all-cause mortality or nonfatal stroke. Patients taking ASA and dipyridamole discontinued trial medication more often than those on ASA alone (34% vs. 26%), mainly because of headache. A recent systematic review and meta-analysis (Wong et al. 2013) included the results of 3 RCTs (ESP-2, ESPRIT & EARLY) examining the risk of stroke recurrence associated with dipyridamole + aspirin vs. aspirin alone. There was a non-significant reduction in the risk of stroke recurrence associated with dual therapy (RR=0.64, 95% CI 0.37-1.10, p=0.80).

A single trial has examined the effectiveness of an non-aspirin comparator as the single agent in a dual agent trial (Sacco et al. 2008). The Prevention Regimen for Effectively avoiding Second Stroke (PRoFESS) trial, randomized 20,332 patients, who had experienced an ischemic stroke within the previous 90 days to receive 25 mg aspirin + 200 mg extended release dipyridamole (ERDP) twice daily or 75 mg clopidogrel daily, for 4 years. There was no difference in the number of patients who experienced stroke, MI or vascular death between group (13.1% in each group, HR=0.99, 95% CI 0.92-1.07). Stroke recurrence rates were similar in both arms of the trial (9.0% among patients assigned to receive ASA plus extended-release dipyridamole and 8.8% among patients assigned to receive clopidogrel; HR 1.01, 95% CI 0.92–1.11). More patients in the ERDP group experienced a major hemorrhagic event (4.1% vs. 3.6%, HR=1.15, 95% CI 1.00-1.32) or an intracranial hemorrhage (0.9% vs. 0.5%, HR=1.08, 95% CI 1.11-1.83).

Antiplatelet Therapy Evidence Tables and Reference List

7. Anticoagulation for Individuals with Stroke and Atrial Fibrillation

Secondary Prevention of Stroke Update 2017	7.Anticoagulation for Individuals with Stroke and Atrial Fibrillation

Note: 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 Canadian Cardiovascular Society Atrial Fibrillation Guidelines 2016: Prevention of Stroke and Systemic Thromboembolism in Atrial Fibrillation and Flutter (October 2016).

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

Nonvalvular** atrial fibrillation **refers to** atrial fibrillation **in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair (CCS 2016).

DOAC – Direct Oral AntiCoagulant

7.1 Detection of Atrial Fibrillation

i. Patients with suspected transient ischemic attack or ischemic stroke should have a 12-lead ECG to assess cardiac rhythm and identify atrial fibrillation or flutter or evidence of structural heart disease (e.g. myocardial infarction, left ventricular hypertrophy) [Evidence Level B].

ii. For patients being investigated for an acute embolic ischemic stroke or TIA of undetermined source, ECG monitoring at least 24 hours 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 acute embolic ischemic stroke or TIA of undetermined source whose initial short-term ECG monitoring does not reveal atrial fibrillation but a cardioembolic mechanism is suspected, prolonged ECG monitoring for at least 2 weeks is recommended to improve detection of paroxysmal atrial fibrillation in selected patients who are not already receiving anticoagulant therapy but would be potential anticoagulant candidates [Evidence Level A].

7.2 Prevention of recurrent stroke in patients with non-valvular atrial fibrillation

i. Patients with transient ischemic attack or ischemic stroke *and* non-valvular atrial fibrillation should receive oral anticoagulation [Evidence Level A].

   a. In most patients requiring anticoagulants for atrial fibrillation, direct non-vitamin K oral anticoagulants (DOAC) such as apixaban, dabigatran, edoxaban, or rivaroxaban should be prescribed in preference over warfarin [Evidence Level A].

   b. For patients already receiving warfarin with good International Normalized Ratio (INR) control (Range 2.0 – 3.0, with TTR >70%), continuing warfarin is a reasonable anticoagulation option [Evidence Level B].

   c. When selecting choice of oral anticoagulants, patient specific criteria should be considered [Evidence level C].

ii. For patients with acute ischemic stroke and atrial fibrillation, routine use of bridging with heparin is not recommended [Evidence Level B].

   a. Bridging with antiplatelet therapy is suggested until the patient is anticoagulated [Evidence Level C]. *Refer to Prevention of Stroke Section 6 on Antiplatelet Therapy for*

Ischemic Stroke and Transient Ischemic Attack for additional recommendations on antithrombotic therapy.

iii. For patients with ischemic stroke or TIA and atrial fibrillation who are unable to take oral anticoagulant therapy (DOAC or warfarin), aspirin alone is recommended [Evidence Level A]. (New for 2017)

   a. The addition of clopidogrel to aspirin therapy, compared with aspirin therapy alone, may be reasonable and decisions should be individualized based on patient bleeding risk [Evidence Level B].

iv. For patients with a mechanical heart valve, warfarin is recommended for stroke prevention with careful INR monitoring; non-vitamin K oral anticoagulants are contraindicated [Evidence Level B].

v. For patients in whom long-term anticoagulant therapy is contraindicated, a left atrial appendage closure procedure may be considered [Evidence Level B].

Clinical Considerations (new 2017):

i. The optimal timing to start anticoagulant therapy after stroke has not been defined by clinical trial evidence, and should be based on individual benefit/risk assessment taking into account the clinical circumstances, infarct size, imaging appearances, age, comorbidities, and estimated stroke recurrence risk.

ii. According to expert consensus, a general approach to the target timing of initiation of oral anticoagulant therapy poststroke is as follows: 1 day post-event after a TIA, 3 days poststroke after a mild stroke, 6 days poststroke after a moderate stroke, and 12 days poststroke after a severe stroke. (*Heidbuchel et al. EHRA practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary. European heart journal. 2013;34(27):2094-2106).*

7.3 Enhancing anticoagulant therapy effectiveness in practice and minimizing bleeding complications

i. Medication adherenceshould be continually assessed and reinforced for patients on all oral anticoagulants at each follow-up visit [Evidence Level B].

   a. For patients with atrial fibrillation taking warfarin, careful dosing and consistent international normalized ratio monitoring is recommended to minimize adverse events; warfarin efficacy is dependent on maintaining therapeutic INR control (INR range 2.0 to 3.0; if presence of mechanical valve range is 2.5 to 3.5), and declines significantly when the international normalized ratio falls below 2.0 [Evidence Level A].

   b. 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].

ii. For patients prescribed apixaban, dabigatran, edoxaban, or rivaroxaban, creatinine clearance should be routinely monitored at least once annually, and when there is a change in health status [Evidence Level C]..

   a. Dose adjustments or a change in selected agent may be required based on changes in renal function if detected.

   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 (e.g., creatinine creatinine) for medication adjustment if required [Evidence Level C].

iii. Concomitant antiplatelet therapy with oral anticoagulant therapy is not routinely recommended in patients with atrial fibrillation due to increased bleeding risk unless there is a specific additional medical indication [Evidence Level B].

Notes: (New 2017)

- *Refer to Canadian Cardiovascular Society 2016 Atrial Fibrillation guidelines for additional information on detection and management of atrial fibrillation http://www.onlinecjc.ca/article/S0828-282X(16)30829-7/fulltext*
- *For peri-operative management of patients on oral anticoagulant therapy, refer to Thrombosis Canada guidelines at http://thrombosiscanada.ca/?page_id=18#*

Rationale

Atrial fibrillation is a significant risk factor for stroke, with one in six patients with ischemic stroke found to have atrial fibrillation. Stroke caused by atrial fibrillation is highly preventable if patients are treated with anticoagulants. Detecting AF following a stroke or transient ischemic attack is important since, once identified, it can be effectively treated. Since most patients do not undergo prolonged screening, AF is often undetected and hence, the condition is generally under-diagnosed.New classes of drugs are available that have demonstrated benefits over previous standard therapy with warfarin.

System Implications

- Increased public awareness of atrial fibrillation as a risk factor for stroke.
- 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).
- A process for appropriate outpatient monitoring of patients' international normalized ratio and follow-up communication with patients taking anticoagulants.
- Optimization of comprehensive strategies at the local, regional and provincial levels to prevent the recurrence of stroke.
- 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.
- For patients taking warfarin, access to a dedicated anticoagulant management clinic is associated with better patient outcomes compared to routine medical care.
- Universal access to cost-effective pharmaceuticals, 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 fibrillationprescribed 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 on 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.

Measurement Notes

- Performance measure 3: reasons why patients with atrial fibrillation and stroke are not on anticoagulants should be collected and reported. These may include contraindications, compliance

issues and physician prescribing patterns, among others. This additional information will help to inform the direction for quality improvement initiatives.

- If there is documentation of atrial fibrillation, the chart should be reviewed for medications prescribed to the patient at the time of discharge, specifically including warfarin, dabigatran, rivaroxaban, apixaban or heparin. Performance measures should be stratified to include proportions prescribed each of these medications.
- Data sources may include discharge summary, history and physical examination, , primary care provider (or physician/nurse practitioner orders, nurses' notes from inpatient chart, stroke prevention clinic documents, and primary care charts.
- To measure whether the patient's International Normalized Ratio was in the therapeutic range, laboratory reports or other reliable documentation are required to verify the International Normalized Ratio levels, and these should be reviewed over a period of time rather than as one single measure.
- Providing a prescription does not ensure patient adherence with medication administration. Adherence can be determined through patient self-report and through International Normalized Ratio measurements over time.
- At this time, adherence to the new oral anticoagulants cannot be objectified in the same way as having INR in therapeutic range

Implementation Resources and Knowledge Transfer Tools

Health Care Provider Information

- Canadian Cardiovascular Society Atrial Fibrillation Guidelines: http://www.onlinecjc.ca/article/S0828-282X(16)30829-7/abstract
- Canadian Cardiovascular Society Atrial Fibrillation Pocket Guide 2016: http://www.ccs.ca/images/Guidelines/PocketGuides_EN/Pocket_Guides/AF_Pocket_Guide_2016.pdf
- Canadian Cardiovascular Society tools (app, slide decks, pocket guides, e-learning): http://www.ccsguidelineprograms.ca/index.php?option=com_content&view=article&id=133:afib-tools-and-resources&catid=81
- How to Monitor Patients Receiving Direct Oral Anticoagulants: Checklist ; Gladstone et al; Annals of Internal Medicine, June 2015 http://annals.org/article.aspx?articleid=2362311 http://thrombosiscanada.ca/?p=1400
- Direct Oral Anticoagulant (DOAC) Follow-Up Checklist and Quick Reference Tables for Clinicians. Available at: http://thrombosiscanada.ca/wp-content/uploads/2016/03/M212-Clinician-tool_v9.pdf
- Thrombosis Canada Perioperative Management Tables for DOACs and Warfarin. Available at: http://thrombosiscanada.ca/?page_id=18

Patient Information

- Atrial Fibrillation - http://www.heartandstroke.ca/heart/conditions/atrial-fibrillation
- Stroke Medications - http://www.heartandstroke.ca/stroke/treatments/medications
- Thrombosis Canada patient information: http://thrombosiscanada.ca/?resourcepage=patient-family-information

Summary of the Evidence 2017

Detecting Atrial Fibrillation

Atrial fibrillation (AF) is a common arrhythmia, which is associated with an increased risk of ischemic stroke. Detecting AF following a stroke or TIA is important since, once identified, it can be effectively treated. However, AF is under-diagnosed because it is frequently paroxysmal and asymptomatic and patients do not routinely undergo prolonged screening. The results from four RCTs and numerous

observational studies have demonstrated that prolonged post-stroke ECG monitoring using wearable or insertable devices is 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. In the Event Monitor Belt for Recording Atrial Fibrillation after a Cerebral Ischemic Event (EMBRACE) trail (Gladstone et al. 2014), a 30-day ambulatory cardiac event monitor was found to be superior to repeat 24-hour Holter monitoring in identifying AF in 572 patients aged 52 to 96 years (mean=72.5 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 in 16.1% of patients, using the cardiac event monitor compared with 3.2% of patients in the Holter group (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. An economic evaluation, based on AF rates and anticoagulation treatment from the EMRACE trial (Yong et al. 2016) suggests that prolonged cardiac monitoring was highly cost-effective ($2,166/QALY). De Angelis et al. (2016) also reported that under certain conditions, cardiac monitoring can be cost-effective. Similar findings were reported in the Cryptogenic Stroke and Underlying AF (CRYSTAL-AF) trial (Sanna et al. 2014) when patients (mean age of 61.5 years) received long-term monitoring with an insertable cardiac monitor (ICM). At 6 months, the rate of detection of AF was significantly higher among patients assigned to the ICM group (8.9% vs. 1.4%, HR=6.4, 95% CI 1.9- 21.7, p<0.001), compared with those who received standard monitoring using ECG monitoring on a schedule at the discretion of their treating physician. Similar results were reported at 12 months (12.4% vs. 2.0%, HR=7.3, 95% CI 2.6- 20.8, p<0.001). The yield of detecting atrial fibrillation with prolonged cardiac monitoring is greatest with increased age. No RCT data is available on individuals under the age of 40 years; the decision to order prolonged cardiac monitoring in young patients could be considered based on clinical circumstances.

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. The Finding Atrial Fibrillation in Stroke - Evaluation of Enhanced and Prolonged Holter Monitoring (FIND-AF) trial randomized 398 patients over age 60 years (average age 73 years) and found that a strategy of 10-day Holter monitoring started within the first week post stroke and repeated at 3 months and 6 months was superior to standard care, which consisted of an average of 73 hours of inpatient telemetry plus an average of 24 hours of Holter monitoring (Wachter et al. 2016). At 6 months, detection of AF was significantly higher in the prolonged monitoring group (13.5% vs. 4.5%; absolute difference 9%, 95% CI 3.5-14.6, p=0.002; NNS=11). Similar findings were reported in the Cryptogenic Stroke and Underlying AF (CRYSTAL-AF) trial (Sanna et al. 2014) when patients (mean age of 61.5 years) received long-term monitoring with an insertable cardiac monitor (ICM). At 6 months, the rate of detection of AF was significantly higher among patients assigned to the ICM group (8.9% vs. 1.4%, HR=6.4, 95% CI 1.9- 21.7, p<0.001), compared with those who received standard monitoring using ECG monitoring on a schedule at the discretion of their treating physician. Similar results were reported at 12 months (12.4% vs. 2.0%, HR=7.3, 95% CI 2.6- 20.8, p<0.001).

The terms valvular and nonvalvular heart disease reflect overly simplistic definitions, and do not sufficiently discriminate disorders with similar pathogenesis of thromboembolisms or thromboembolic risk, and importantly do not clearly define treatment needs (De Caterina et al. 2014, Macle et al. 2015). While phase III studies comparing individual novel oral anticoagulants (NOACs) with warfarin used variable

definitions of valvular atrial fibrillation, more accurate definitions are being sought to better guide treatment for patients who should not be treated with a NOAC. Severe mitral stenosis and mechanical heart valves are the only conditions where there is consensus regarding the avoidance of anticoagulation with NOACs. Data are limited from any of the pivotal NOAC trials to provide clear reassurance with regards to the treatment of other cardiac disorders, especially severe native valvular lesions that might merit anticoagulant prophylaxis (De Caterina et al. 2014, Di Biase 2016). The 2016 update of the Canadian Cardiovascular Society guidelines for the management of atrial fibrillation state that "the use of NOACs is contraindicated in the presence of mechanical heart valves, rheumatic mitral stenosis, or moderate and severe nonrheumatic mitral stenosis".

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 TIA). 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 observational study, Patient-Centered Research into Outcomes Stroke Patients Prefer and Effectiveness Research (PROSPER, Xian et al. 2015) included 12,552 patients with acute ischemic stroke and documented persistent or paroxysmal AF/flutter who were admitted to hospitals in the United States from 2009-2011. The risk of major cardiovascular evets among those discharged with warfarin was compared with those not treated with any oral anticoagulant. Over the following 2 years, fewer patients discharged on warfarin experienced a major event (54.7% vs. 66.8%; HR=0.87, 99% CI 0.78-0.98, p=0.003) and spent more days at home (47.6 days, 99% CI 26.9-68.2, p<0.001).

The Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study recruited 973 patients (12.5% with previous stroke or TIA 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 anti-coagulants with antiplatelet therapy in individuals with non-rheumatic (non-valvular) AF and history of previous stroke or TIA. Two RCTs were included. The European Atrial Fibrillation Trial (EAFT) included 455 patients within three months of TIA 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 TIA 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

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. The landmark Randomized Evaluation of Long-term anticoagulant therapy (RE-LY) trial (Connolly et al. 2009), 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 TIA/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 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). It should be noted that patients in the warfarin group had a therapeutic INR only about 64% of the time, which is consistent with other clinical trials. To achieve a stroke rate similar to the dabigatran 150 mg twice daily group, it is estimated that patients assigned to warfarin in RE-LY needed to have a therapeutic INR 80% of the time, a degree of control unlikely to be achieved in clinical trials or clinical practice.

In a long-term extension of the RE-LY trial (Connolly et al. 2013), 5,851 pparticipants who had been assigned to either of the dabigatran dosing schedules in the original trial could continue in the RELY-ABLE study if they did not discontinue study medication at trial termination. Participants continued to receive the same dose of dabigatran (still blinded to the dose condition) as they had throughout the original trial. Patients enrolled in the warfarin condition did not continue in the trial. Median duration of follow-up for the patients enrolled in RELY-ABLE was 5.5 years. During the study period, 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). Dyspeptic symptoms were reported in approximately 5% of

patients in each group. In subgroup analysis, Diener et al. (2010) examined treatment effects between patients with and without previous history of stroke or TIA. No interactions were reported for any of the outcomes of interest, including stroke, ICH, ischemic or unknown stroke, disabling or fatal stroke, MI, vascular death, or death from any cause.

Three Factor Xa inhibitors, rivaroxiban, apixaban and edoxaban (recently approved in Canada), have been investigated in large clinical trials. 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 rivaroxiban (20 mg daily or 15 mg daily in patients with reduced creatinine clearance) or adjusted-dose warfarin (target INR pf 2.0 to 3.0). The median length of treatment was 590 days. Stroke or systemic embolism occurred less frequently in patients who received rivaroxiban (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), while the risk of major bleeding from a gastrointestinal site was increased (3.2% vs. 2.2%, p<0.001). A post hoc analysis from the ROCKET-AF trial demonstrated no significant difference in treatment effectiveness or risk for adverse events between groups of individuals with or without previous stroke or TIA, suggesting that rivaroxaban may be considered as a potential alternative to warfarin in secondary prevention of stroke (Hankey et al. 2012).

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. In the subgroup analysis of patients with previous stroke or TIA (Easton et al. 2012), the rate of stroke or systemic embolism was similar between groups (2.46 per 100 patient-years of follow-up in the apixaban vs. 3.24 in the warfarin group; HR= 0.76, 95% CI 0.56-1·03, p for interaction=0·71).

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.
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. Blinding was maintained throughout the study by using sham INR values for the edoxaban group and by giving all patients a placebo tablet in addition to their active medication. 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).

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 TIA 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 2 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 2 TIAs in the dabigatran group and 0 strokes and 2 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 or Anticoagulation Following Ischemic Stroke

Results from the Early Recurrence and cerebral bleeding in patients with acute ischemic stroke and Atrial Fibrillation (RAF) study (Paciaroni et al. 2015) 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, TIA, 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).

Atrial Fibrillation and Stroke Evidence Tables and Reference List

8. Management of Extracranial Carotid Disease and Intracranial Atherosclerosis

Secondary Prevention of Stroke *Update 2014*
8. Management of Extracranial Carotid Disease and Intracranial Atherosclerosis

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

8.1 Symptomatic Carotid Stenosis

i. Patients with recent transient ischemic attack or non-disabling stroke and ipsilateral **50 to 99** percent symptomatic carotid stenosis should have an evaluation by an individual with stroke expertise and selected patients should be offered carotid endarterectomy (revascularization) as soon as possible [Evidence Level B].

ii. Carotid stenosis should ideally be measured by CTA to guide surgical decision-making [Evidence Level C].

iii. In individuals with non-disabling stroke or transient ischemic attack and **70-99** percent symptomatic carotid stenosis, carotid endarterectomy should be performed [Evidence Level A], on an urgent basis.

   a. Ideally carotid endarterectomy should be performed within the first days following non-disabling stroke or transient ischemic attack [Evidence Level B] and within 14 days of ischemic event onset for patients who are not clinically stable in the first few days [Evidence Level A]. *Refer to Table below for summary of recurrent stroke risk at various time points*

iv. Carotid endarterectomy should be performed by a surgeon/centre that routinely audits their performance results, especially perioperative stroke and death rates. 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].

v. Carotid endarterectomy is generally more appropriate than carotid stenting 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].

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

   a. Carotid stenting should be performed by an interventionist/centre with expertise that routinely audits their performance results, especially perioperative stroke and death rates. The randomized trial upon which these recommendations are based involved combined periprocedural stroke and death rates of 5% [Evidence Level B].

8.2 Asymptomatic and Remotely Symptomatic Carotid Stenosis

i. Patients with symptoms of TIA and non-disabling stroke who are found to have an asymptomatic carotid stenosis should be evaluated by a physician with expertise in stroke management [Evidence Level C].

ii. Stroke patients with asymptomatic carotid stenosis should receive aggressive medical management of risk factors as defined throughout the *Secondary Prevention of Stroke* Module (for example, blood pressure, cholesterol, antiplatelet therapy lifestyle changes) [Evidence Level B].

iii. Carotid endarterectomy may be considered for selected patients with 60 to 99 percent carotid

stenosis who are asymptomatic or were remotely symptomatic (i.e., greater than six months) [Evidence Level A].

a. 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].

b. 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 A].

iv. Carotid stenting may be considered in patients with 60 to 99 percent 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].

8.3 Intracranial Stenosis

i. Intracranial stenting is not recommended for the treatment of recently symptomatic intracranial 70% to 99% stenosis [Evidence Level B].

ii. Based on the SAMMPRIS trial (Derdeyn C et al. 2014), the medical management arm included dual antiplatelet therapy with ASA 325 mg and Clopidogrel 75 mg started within 30 days of stroke or TIA and treated for up to 90 days [Evidence Level B], and should be considered for each patient on an individual basis. In addition, there should be aggressive management of all vascular risk factors including blood pressure, lipids, diabetes mellitus, and other at-risk lifestyle patterns [Evidence Level A].

iii. 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 clear evidence to guide further management decisions; intracranial angioplasty (with or without stenting) may be reasonable in carefully selected patients [Evidence Level C].

8.4 Cervicocephalic Artery Dissection

i. A diagnosis of carotid or vertebral dissection can be established by CTA, MRA or DSA [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 or carotid dissection originating above the angle of the jaw.

ii. Antithrombotic therapy for stroke prevention is recommended for individuals with a diagnosis of an extracranial carotid or vertebral artery dissection [Evidence Level B].

a. There is uncertainty about the comparative efficacy of antiplatelet therapy vs. anticoagulation with heparin or warfarin; either treatment is considered reasonable and decision should be based on individual risk/benefit analysis [Evidence Level B].

b. There is a lack of evidence regarding the optimal duration of antithrombotic therapy and the role of repeat vascular imaging in decision-making. Decisions may be based on individual clinical factors [Evidence Level C].

c. *Note: There is insufficient evidence at this time to make a recommendation regarding the use of DOACs in patients with arterial dissections*.

iii. There is a lack of evidence regarding the use of anticoagulation in intracranial arterial dissection. Decisions may be based on individual clinical factors [Evidence Level C].

Refer to Section One for recommendations on urgent vascular imaging in patients with acute TIA and

non-disabling stroke.

Refer to Section 2 on aggressive prevention management, including lifestyle and 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 nine patients with symptomatic severe (70 to 99 percent) carotid stenosis treated with carotid endarterectomy). 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.

System Implications

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

Performance Measures

1. Proportion of stroke or TIA patients with moderate to severe (50 percent to 99 percent) symptomatic carotid artery stenosis who undergo a carotid revascularization procedure following an index stroke/TIA event. (KQI)
2. Proportion of stroke/TIA 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 TIA 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 incident stroke event.
6. Proportion of stroke patients with mild carotid stenosis (less than 50 percent) who undergo carotid intervention procedure following the incident 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

- 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.
- The stroke onset time will depend on patient report or that of a reliable observer at the time of the event.
- 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.
- Data source for surgical date should be surgical note, nurses' notes and discharge summary.
- 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

- Question and Answers about carotid endarterectomy NINDS: http://www.ninds.nih.gov/disorders/stroke/carotid_endarterectomy_backgrounder.htm
- Online risk calculator from OXVASC – I year and 5 year predictions – add to resource sectionhttp://www.stroke.ox.ac.uk/

Patient Information

- National Heart, Lung and Blood Institute: http://www.nhlbi.nih.gov/health/health-topics/topics/carend/

Summary of the Evidence 2017

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 (CAS) has emerged as an alternative to carotid endarterectomy in patients at high risk for complications for endarterectomy such as contralateral occlusion or severe coronary artery disease. The percutaneous approach also avoids the risks of general anaesthesia and the local complications of neck haematoma, 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). The final results of this trial have been published recently (Derdeyn et al. 2014). The median follow-up period was 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).

Carotid Artery Stenting (without embolic protection) vs. Carotid Endarterectomy
The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) included 504 patients with symptomatic or asymptomatic carotid artery stenosis of ≥30%, considered to require revascularisation and suitable for surgery or endovascular treatment (Brown et al. 2001). Patients were randomized to endovascular treatment with balloon angioplasty with or without stent insertion or CEA. Stents were used in 55 patients. At the time the trial was conducted, no protection devices were available. The median delay from randomization to surgery was 20 days (endovascular treatment) and 27 days (CEA). Mean length of follow-up was 2 years. There were no differences between groups (endovascular treatment vs. CEA) including death (3% vs. 2%), disabling stroke (4% vs. 4%), non-disabling stroke (4% vs. 4%), death or disabling stroke (6% vs. 6%) or death or any stroke (10% vs. 10%) within 30 days. At one year following treatment, severe carotid stenosis (70%-99%) was more common in patients who had received endovascular treatment (14% vs. 4%; p<0.001). In a long-term follow-up study (Ederle et al. 2009), the 8-year cumulative incidence of disabling stroke or death was non-significantly higher in the endovascular treatment group (45.2% vs. 50.4%, HR=1.02, 95% CI 0.79-1.32) as was the combined outcome of non-perioperative stroke or TIA (HR=1.37, 95% CI 0.95-1.97).

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).

Carotid Artery Stenting (with embolic protection) vs. Carotid Endarterectomy
Several randomized trials that directly compared the safety of CEA with CAS (with protection) among patients who were symptomatic and/or asymptomatic have been published. The results from most of them suggest that during long-term follow-up, stenting is as effective as CEA.

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).

A Cochrane review (Bonati et al. 2012) included 16 trials of patients with symptomatic stenosis, who had experienced a minor stroke, asymptomatic stenosis or both asymptomatic and symptomatic carotid stenosis. The treatment contrasts included any CEA procedure vs. any endovascular technique. Endovascular therapy was associated with a higher risk of death or any stroke within 30 days of treatment (OR=1.72, 95% CI 1.29- 2.31, p<0.0003), and death or any stroke between randomization and 30 days after treatment or ipsilateral stroke until the end of follow-up. The risk was highest in the group of studies with follow-up of 2.4 years, or longer. There was no difference between treatment groups for the outcomes of death or major or disabling stroke between randomization and 30 days after treatment (OR=1.28, 95% CI 0.93-1.77, p=0.13) or any stroke between randomization and 30 days after treatment (OR=1.21, 95% CI 0.36- 4.04, 9=0.76), although the risk was increased among the subgroup of patients at standard surgical risk, who received endovascular treatment. Endovascular therapy was associated with a reduced risk of cranial nerve palsy within 30 days of surgery and access site hematoma (OR=0.37, 95% CI 0.18- 0.77, p= 0.0082). The authors suggested that while endovascular treatment was associated with an increased risk of peri-procedural stroke or death compared with endarterectomy, the excess risk may be limited to older patients. The results from another meta-analysis, examining the same treatment contrasts, and using the results from 13 RCTs reported that compared with CEA, stenting was associated with an increase of 19 strokes and 10 fewer MIs for every 1000 patients treated (Murad et al. 2011).

Cervical Artery Dissection

While the incidence of cervical artery dissections (CAD) is relatively low, estimated to be between 2.6 to 2.9 per 100,000, CAD is over-represented among persons less than 45 years (Weimar et al. 2010). Given the increased risk of recurrent stroke associated with CAD, 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* (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. 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: **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 (TIA 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

9. Concurrent Cardiac Issues in Individuals with Stroke

Secondary Prevention of Stroke **9. Cardiac Issues and Stroke**
Update 2017

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

9.1 Patent Foramen Ovale (PFO) *(Revised 2017)*

i. Patients with a recent ischemic stroke or TIA attributed to a PFO should have an evaluation by clinicians with stroke and cardiovascular expertise [Evidence Level C].

ii. For carefully-selected patients with a recent ischemic stroke or TIA 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 or a TIA with positive neuroimaging or cortical symptoms;

   c. The patient has been evaluated by a neurologist or clinician with stroke expertise, and the PFO is felt to be the most likely cause for the index stroke event following a thorough etiological evaluation to exclude alternate etiologies.

iii. For patients requiring long-term anticoagulation, the decision regarding PFO closure remains unclear, and decisions should be based on individual patient characteristics and risk versus benefit profile [Evidence C].

iv. For patients with a recent ischemic stroke or TIA attributed to a PFO who do no 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].

v. There is insufficient evidence to make a recommendation regarding the comparative effectiveness of PFO closure vs. anticoagulant therapy.

9.2 Paediatric Stroke and Patent Foramen Ovale

i. The significance of a PFO and optimal treatment of paradoxical embolism associated with PFO in a child with ischemic stroke is not known [Evidence Level C].

ii. There is insufficient research evidence in children with ischemic stroke to support closure of patent foramen ovale [Evidence Level C].

9.3 Aortic Arch Atheroma:

i. Aortic arch atheroma should be managed by optimizing 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 aspirin and clopidogrel compared to warfarin; the effectiveness of anticoagulant therapy compared with antiplatelet therapy is uncertain, and the choice should be individualized [Evidence Level B].

9.4 Heart Failure, Decreased Ejection Fraction, Thrombus

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

ii. In patients with ischemic stroke or transient ischemic attack in sinus rhythm with severe left ventricular dysfunction (ejection fraction ≤35%) without evidence of left atrial or left ventricular thrombus, the net benefit of anticoagulant therapy compared with antiplatelet therapy is uncertain, and the choice of management strategies should be individualized [Evidence Level B].

iii. The risk of stroke, including recurrent stroke, is increased by the presence of heart failure therefore individuals with stroke or transient ischemic attack and heart failure should be managed with aggressive stroke prevention therapies [Evidence Level B]. *Refer to all other Sections of this Secondary Prevention of Stroke for additional information.*

Rationale

For many years, the role of percutaneous closure of a patent foramen ovale (PFO) for secondary stroke prevention was controversial for several reasons. While PFOs are known to be common in the general population (25%), they are often incidental rather than pathogenic, and the results from previous RCTs were inconclusive. In 2017, the publication of two new RCTs and long-term follow-up of an earlier one, (Saver JL, Carroll JD, Thaler DE, et al, 2017) demonstrated that among carefully-selected patients, PFO closure was superior to medical therapy for prevention of stroke recurrence.

There is also a relationship between stroke and other cardic conditions including aortic atheroma and heart failure. Comprehensive care of these patients by experts in stroke and in heart disease is required ot optimize outcomes.

System Implications

- Support for ongoing research into etiology for patients with cryptogenic stroke.
- Support for research to further investigate the impact of PFO closure versus medical therapy.

Performance Measures

Ongoing collection of epidemiological data on prevalence of PFO in individuals with stroke is recommended.

Implementation Resources and Knowledge Transfer Tools

Health Care Provider Information

- Thrombosis Canada
  http://thrombosiscanada.ca/?resourcepage=resources-2
- Canadian Cardiovascular Society
  http://www.ccs.ca/en/
- Heart failure
  http://www.chfn.ca/
- Paediatric Stroke program
- http://www.perinatalstroke.com/
- Sick Kids Children's Stroke Program
- http://www.sickkids.ca/Psychology/Education-and-learning/Predoctoral-internship-program/Specific-rotation-descriptions/Childrens-Stroke-Program.html
- Your Stroke Journey: A guide for people living with stroke
  http://www.strokebestpractices.ca/wp-content/uploads/2015/03/YOURSTROKEJOURNEY.FINAL_.ENGLISH..pdf
- Post Stroke Checklist

http://www.strokebestpractices.ca/wp-content/uploads/2014/06/HSF%20Post%20Stroke%20Checklist_WEB.pdf

- Canadian Cardiovascular Harmonized National Guidelines Endeavour (C-CHANGE): 2014 update http://www.cmaj.ca/content/186/17/1299.full

Patient Information

- Patent Foramen Ovale: http://www.stroke.org/site/PageServer?pagename=PFO
- Patent Foramen Ovale: http://my.clevelandclinic.org/heart/disorders/congenital/pfo.aspx
- Patent Foramen Ovale: http://www.childrenshospital.org/conditions-and-treatments/conditions/patent-foramen-ovale/symptoms-and-causes
- Congenital heart defects http://www.heart.org/HEARTORG/Conditions/CongenitalHeartDefects/Congenital-Heart-Defects_UCM_001090_SubHomePage.jsp

Summary of the Evidence 2017

Patent foramen ovale (PFO)
Individuals with PFOs may be at increased risk of stroke and stroke recurrence, particularly in younger patients (<60 years of age) with stroke of unknown etiology. Although surgical closure has been used for patients with this condition, until recently, its effectiveness remained in question. 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 TIA 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 more recent studies from the CLOSE (Mas et al. 2017) and REDUCE (Sondergaard et al. 2017) trials and long-term results of the RESPECT trial (Saver et al. 2017) have demonstrated that among carefully-selected patients, PFO closure was superior to medical therapy for prevention of stroke recurrence. In the CLOSE trial, Mas et al. (2017) recruited 633 young patients (mean age approximately 43 years) who had experienced a recent stroke with no identifiable cause other than a PFO, which had to be associated with either an atrial septal aneurysm (excursion >10 mm) or a large interatrial shunt (>30 microbubbles in the left atrium within three cardiac cycles after opacification of the right atrium). After a mean duration of follow-up of 5.3, there were no strokes in patients randomized to the PFO closure group compared with 6.0% in the antiplatelet-only group, who received mainly 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%. The frequency of atrial fibrillation was significantly higher in the PFO group (4.6% vs. 0.9%, p=0.02). The REDUCE trial (Sondergaard et al. 2017) enrolled 664 patients (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. The risk of ischemic stroke was significantly lower in the PFO closure group after a median duration of follow-up of 3.2 years (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). Finally, in long-term follow-up of the RESPECT trial, after a median duration of follow-up of 5.9 years, the risk of recurrent ischemic stroke was significantly lower in the PFO closure group (3.6% vs. 5.8%; HR=0.55, 95% CI 0.31-0.999, p=0.046). 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).

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. The Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial included 2,305 patients with left ventricular ejection fraction (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 sub group 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. In two trials, the treatment contrasts included a placebo or no treatment arm (Cokkinos et al., 2006 and Cleland et al. 2004). In neither study were there significant differences between study groups for the primary outcome, which included stroke and death.

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, TIA, 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).

Cardiac Issues and Stroke Evidence Tables and Reference List

APPENDIX ONE

Canadian Stroke Best Practice Recommendations
STROKE PREVENTION WRITING GROUP 2017:

NAME	PROFESSIONAL ROLE	LOCATION	DECLARED CONFLICTS OF INTEREST
Wein, Theodore	Co-Chair, Assistant Professor of Neurology and Neurosurgery, McGill University Stroke Prevention Clinic, Montreal General Hospital	Quebec	**Potential Conflict:** BoehringherIngelheim **Nature of Relationship** Research, Speaker, Travel **Potential Conflict:** Bayer **Nature of Relationship** Research, Speaker, Travel **Potential Conflict**: Allergan Inc **Nature of Relationship** Research, Consultant, **Potential Conflict:** Servier **Nature of Relationship** Research, Speaker
Gladstone, David	Associate Professor, Department of Medicine (Neurology), University of Toronto; Director, Regional Stroke Prevention Clinic, Sunnybrook Health Sciences Centre, Toronto	Ontario	**Potential Conflict:**Bayer, Boehringer-Ingelheim, Bristol Myers Squibb, Pfizer **Nature of Relationship:** speaker fees for CME events and/or honouraria for advisory boards **Potential Conflict:** EMRACE trial and SCREEN-AF trial **Nature of Relationship** Principal Investigator
Côté, Robert	Stroke Neurologist, Professor, Department of Neurology, Neurosurgery and Medicine; McGill University Health Centre	Quebec	**Company/Organization Name** Pfizer/BMS **Nature of Relationship** Speaker honorarium **Potential or Actual Conflict of Interest** Area of oral anticoagulants
Berlingieri, Joseph	Internist and Intensivist; Medical Co-Director of JBN Medical Diagnostic Services (private stroke prevention clinic in Burlington, linked to Hamilton stroke program; brings community perspective)	Ontario	**No conflicts to declare**
Bourgoin, Aline	Stroke Prevention Coordinator, Nurse Specialist Stroke Prevention Clinic Champlain Regional Stroke Network,	Ontario	**No conflicts to declare**
Buck, Brian H.	Vascular Neurologist, Assistant Professor, Division of Neurology, Department of Medicine, University of Alberta	Alberta	**Company/Organization Name**: Bayer **Nature of Relationship**: Speaker honorarium, advisory board **Potential or Actual Conflict of Interest** Area of oral anticoagulants

Cox, Jafna	Cardiologist; Heart and Stroke Foundation of Nova Scotia Endowed Chair in Cardiovascular Outcomes Research Professor of Medicine and of Community Health and Epidemiology, Dalhousie University	Nova Scotia	**Potential conflict for the following:** **Company/OrganizationName** Bayer (relationship to until present) **Nature of Relationship** Funded research, speaker, advisory board member **Company/Organization Name** BoehringerIngelheim (no relationship for 3 years) **Nature of relationship** Speaker, Advisory Board Member **Company/Organization Name** BMS Pfizer, no relationship for less than 1 year **Nature of relationship** Speaker, Advisory Board Member
Davidson, Dion	Vascular Surgeon Valley Regional Hospital	Nova Scotia	**No conflicts to declare**
Douketis, Jim	Internist and Thrombosis Specialist; Divisions of General Internal Medicine, Hematology and Thromboembolism, McMaster University Department of Medicine; President of Thrombosis Canada (www.thrombosiscanada.ca)	Ontario	Participant in Advisory Boards or Educational Activities for following companies: Bayer (2010-2015); Bristol-Myers-Squibb (2012-2014); Sanofi (2014-2015); Astra-Zeneca (before 2008); Boehringer-Ingelheim (2010-15); Pfizer (2011-15); Biotie (2013); Portola (2012); The Medicines Co. (2012-2013); Daiichi-Sankyo (2015). Consultant to following companies Actelion (2014); AGEN Biomedical (2004-06); Ortho-Janssen Pharmaceuticals (2007-08); Boehringer-Ingelheim (2009-10); Janssen Pharmaceuticals (2014-present); Grant support from following companies: Boehringer-Ingelheim (2014)
Falconer, John	Internist; UBC Clinical Associate Professor of Medicine; Director Kelowna General Hospital TIA/Stroke Unit; Course Director Foundations of Medicine UBC Southern Medical Program	British Columbia	**No conflicts to declare**
Field, Thalia	Stroke Neurologist; Assistant Professor, Faculty of Medicine, University of British Columbia Stroke Neurologist, Vancouver Stroke Program	British Columbia	**Potential Conflict:** Bayer Canada and Bayer Global **Nature of Relationship:** Advisory Board and Speakers' Bureau, research methodology training program participation **Potential Conflict:** BoehringerIngleheim

			Nature of Relationship Funded research
Gioia, Laura	Stroke Neurologist Assistant Professor Department of Neurosciences, CHUM-Centre Hospitalier de l'Université de Montréal Hôpital Notre Dame	Quebec	**Potential Conflict:** Bayer Canada and Bayer Global **Nature of Relationship:** Advisory Board
Habert, Jeffrey	Family Physician, Assistant Professor, University of Toronto, Dept. Of Family And Community Medicine	Ontario	**Potential Conflict: Bayer, Bristol-Myers-Squibb, Boehringer-Ingelheim, Pfizer, Eli-Lilly, Astra-Zeneca, Janssen, Novo-Nordisk** **Nature of relationship: Advisory Board/Speaker**
Jaspers, Sharon	Nurse Practitioner, Stroke Prevention Clinic, Thunder Bay Regional Health Sciences Centre Faculty, Northern Ontario School of Medicine	Ontario	**Potential Conflict:** Bayer,BoehringerIngelheim, Pfizer **Nature of Relationship:** speaker/workshop: honorarium
Lum, Cheemun	Neuroradiologist; Section Head, Interventional Neuroradiology, The Ottawa Hospital	Ontario	**No conflicts to declare**
McNamara Morse, Dana	Nurse Practitioner, Stroke Program, Valley Regional Hospital	Nova Scotia	**No conflicts to declare**
Pageau, Paul	Emergency Physician, The Ottawa Hospital Assistant Professor, Department of Emergency Medicine, The University of Ottawa	Ontario	**No conflicts to declare**
Rafay, Mubeen	Paediatric Stroke Neurologist, Winnipeg Children's; University of Manitoba; Paediatric Stroke Writing Group	Manitoba	**No conflicts to declare**
Rodgerson, Amanda	Clinical Stroke Dietitian Provincial Acute Stroke Unit and Provincial Rehabilitation Unit, Queen Elizabeth Hospital	PEI	**No conflicts to declare**
Semchuk, Bill	Manager, Clinical Pharmacy, Clinical Pharmacist, Regina Lipid Clinic; Regina Qu'Appellle Health Region	Saskatchewan	**Potential Conflict,** Paid Speaker for: BoheringerIngelheim, Bayer and BMS Pfizer
Shoamanesh, Ashkan	Stroke Neurologist; Assistant Professor of Medicine (Neurology); Director, Stroke	Ontario	**Potential Conflict:** Bayer HealthCare Pharmaceuticals **Nature of Relationship** Research Stipend

	Fellowship Program; Marta and Owen Boris Chair in Stroke Research and Care McMaster University / Population Health Research Institute		for Ongoing Committee Involvement in the NAVIGATE ESUS trial
Tamayo, Arturo	Stroke Neurologist; Brandon Regional Hospital, Winnipeg Health Sciences Centre; University of Manitoba	Manitoba	**Potential conflict,** Speaker for**:** Bayer, BoehringerIngelheim and Bristol-Myers Squibb

APPENDIX TWO:

Canadian Stroke Best Practice Recommendations

Secondary Prevention of Stroke

External Reviewers 2017

External Reviewer	Professional Role	Location	Declared Conflicts of Interest
Dr. Natan Bornstein	Professor of Neurology at the Tel-Aviv University, Sackler Faculty of Medicine Head of Stroke Unit at the Tel-has Aviv Medical Center	Israel	**Company/Organization Name** Pfizer Israel **Nature of relationship** Consultation fees **Company/Organization Name** Bayer Israel **Nature of relationship** Consultation fees **Company/Organization** Boehringer Ingelheim Israel **Nature of relationship** Lecture Bureau **Company/Organization** Amgen **Nature of relationship** Advisory Board- Honorarium
Dr. Seemant Chaturvedi	Professor of Clinical Neurology; Vice Chair Neurology Programs; Miami VA Medical Center; Stroke Division	United States	**Potential Conflicts Company/Organization Name** Boehringer Ingelheim **Nature of relationship** Funded researcher
Dr. Marion Cornish	Internist, Critical Care and Geriatric Medicine; Valley Regional Hospital Nova Scotia	Nova Scotia	
Dr. Jamsheed Desai	Stroke, Neuromuscular and General Neurology, Trillium Health Partners Mississauga; Assistant Professor at McMaster University and Lecturer at the University of Toronto.	Ontario	**Potential Conflict Company/Organization Name** Bristol-Myers Squibb **Nature of relationship** CME events, paid speaker
Dr. Robert Hart	Professor of Medicine in the Division of Neurology at McMaster University; Staff Physician at	Ontario	**Potential Conflicts Company/Organization Name** Bayer AG **Nature of Relationship** Sponsored research with personal

	Hamilton Health Sciences, Hamilton General Hospital; Senior Scientist at Population Health Research Institute		stipend; consultancy. **Company/Organization Name** Bristol Myers-Squibb **Nature of Relationship** sponsored research with personal stipend
Dr. Adam Kirton	Associate Professor, Pediatrics and Clinical Neurosciences, Faculty of Medicine, University of Calgary, Alberta Children's Hospital Research Institute (ACHRI), Director Calgary Pediatric Stroke Program Pediatric	Alberta	No conflicts
Dr. Lewis B. Morgenstern	Associate Chair of Neurology for Faculty Development and Finance; Director of the Stroke Program; Professor of Neurology, Epidemiology, Emergency Medicine and Neurosurgery; The University of Michigan Medical School and School of Public Health	United States	No conflicts
Michelle Slapkauskas	RN BScN; Belleville General - Stroke Prevention Clinic	Ontario	No conflicts
Dr. David Spence	MD, FRCPC Professor of Neurology and Clinical Pharmacology Director, Stroke Prevention & Atherosclerosis Research Centre (SPARC) Robarts Research Institute	Ontario	No conflicts
Dr. Luciano A. Sposato	MD, MBA; Associate Professor of Neurology; University of Western Ontario	Ontario	**Potential conflicts** **Company/Organization Name** Boehringer Ingelheim **Nature of relationship** Speaker
Thomas Stewart	Manager, Pre-Admission and Stroke Prevention Clinic Regina Saskatchewan	Saskatchewan	No conflicts

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.

	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	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 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 Max: 30 mg/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	0.5 mg once daily x 3 days then 0.5 mg BID x 4 days then 0.5-1 mg BID x 12 weeks. Begin 1-2 weeks prior to selected quit date.
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				Must titrate dose when discontinuing	Upward titration to reduce nausea from drug

	Nicotine patch	Nicotine gum	Nicotine inhaler	Nicotine Lozenge	Bupropion	Varenicline
	as they are receiving nicotine via the patch/gum/lozenge/inhaler and should be smoking fewer cigarettes, which is the goal.					
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 rending product useless. Rotate patch site to avoid skin irritation.	Recent food and beverage impairs 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 impairs 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 adverse effects if combined with NRT
Contraindications/ Cautions	Life-threatening arrhythmias, severe angina, atopic/eczematous dermatitis or other skin conditions (e.g. psoriasis)	Life-threatening arrhythmias, severe angina	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 other 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. Requires dose adjustment in renal/hepatic disease.	Data not available in pregnancy/lactation. May be considered in adolescents. Requires dose adjustment in renal disease (if CrCl<30mL/min, max 0.5 mg BID).

	Nicotine patch	Nicotine gum	Nicotine inhaler	Nicotine Lozenge	Bupropion	Varenicline
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 (nicotine replacement therapy). 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	$125

**** 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 pubictaion of these recommendations, Canadian product monographs have not changed.*