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CANADIAN BEST PRACTICE RECOMMENDATIONS FOR STROKE CARE

The Canadian Best Practice Recommendations for Stroke Care are intended to provide up-to-date evidence-based guidelines for the prevention and management of stroke. The goal of disseminating and implementing these recommendations is to reduce practice variations in the care of stroke patients across Canada, and to reduce the gap between knowledge and practice. Recommendations are updated every two years to ensure they continue to reflect contemporary stroke research evidence and leading expert opinion. Each update involves critical review of the current medical literature, which informs decisions regarding modification of the recommendations and the performance measures used to assess their impact. Every attempt is made to coordinate with other Canadian groups who are developing guidelines that relate to stroke, such as hypertension, atrial fibrillation and diabetes.

This is the fourth edition of the Canadian Best Practice Recommendations for Stroke Care, which was first released in 2006. The theme of the 2012 – 2013 update is TAKING ACTION, and stresses the critical role and responsibility of healthcare providers at every stage of the continuum of care to ensure that best practice recommendations are implemented and adhered to. TAKING ACTION will lead to optimal outcomes for each stroke patient by providing the best care within the most appropriate setting. This includes rapid and efficient access to diagnostic services, stroke expertise and medical and surgical interventions, rehabilitation and support for ongoing recovery and community reintegration.

TAKING ACTION requires a committed team approach and strong coordination of care across regions and networks, with pre-hospital, acute care, rehabilitation and community-based healthcare providers working together to ensure optimal outcomes for patients and their families, regardless of geographic location.

TAKING ACTION also applies to patients who have experienced a stroke, their families and informal caregivers. Stroke patients and their families need to actively participate in their recovery and openly communicate with their healthcare team. Patients and families must participate in setting the goals they want to achieve during recovery from a stroke, and share concerns, as well as physical, mood and cognitive issues with their team, which will lead to the care required for optimal recovery in all aspects of health.

SECTION 2.0 PREVENTION OF STROKE OVERVIEW

TAKING ACTION FOR THE PREVENTION OF STROKE

TAKING ACTION is an imperative within primary and secondary stroke prevention and applies to systems of care, healthcare providers, patients and the broader community. The primary underpinnings of 'prevention' require TAKING ACTION to prevent first stroke or transient ischemic attack or recurrence of a cerebrovascular event. The actions required to prevent first and recurrent stroke include rapid access to specialized stroke prevention services; promotion of healthy lifestyles to minimize vascular risk; aggressive risk factor management, especially even the slightest elevation in blood pressure; appropriate prescription of medications for prevention; patient compliance with medication regimes and lifestyle changes such as diet and smoking cessation; timely access to interventions such as carotid endarterectomy; and, screening of appropriate patients for smoking status, mood, cognition and sleep difficulties.

TAKING ACTION in stroke prevention involves healthcare providers, policy makers, patients and the public. A critical component of stroke prevention is access to specialized stroke prevention services, 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 diagnostics and interventions, and provide education to patients and families. They also promote continuity of care between acute care facilities, the patient and their primary care providers.

Recent reports on the quality of stroke services across Canada and within specific provinces have shown that there is an insufficient number of stroke prevention clinics or similar services, even in urban areas where large volumes of stroke patients reside, and even fewer in rural settings. Establishing stroke prevention clinics and services within all regions of care is an imperative in TAKING ACTION for stroke prevention.
HIGHLIGHTS OF THE PREVENTION OF STROKE 2012 UPDATE

The 2012 update of the Stroke Prevention Chapter of the Canadian Best Practice Recommendations for Stroke Care reinforces the growing and changing body of research evidence available to guide stroke prevention services. Aggressive risk factor management is emphasized throughout this chapter.

Highlights of the moderate and significant updates to stroke prevention recommendations for 2012 include:

- the potential stroke risk of oral contraceptives and hormone replacement therapy, especially in patients who also smoke;
- continued emphasis on the important role of blood pressure for stroke, and diligent monitoring and treatment to keep blood pressure levels well below 140 mm Hg systolic and 90 mm Hg diastolic;
- alignment of diabetes and stroke recommendations with updated guidelines by the Canadian Diabetes Association; revisions to the lipid management section to reflect ongoing analysis and interpretation of the SPARCL trial;
- the release of the findings from the ASA versus ASA + clopidogrel arm of the SPS3 study that reinforced recommendations advising against the use of dual-antiplatelet therapy;
- anticoagulant therapy recommendations for patients with atrial fibrillation and stroke have been significantly revised to reflect the release of the new classes of anticoagulants, based on the RE-LY (dabigatran), ROCKET (rivaroxaban) and ARISTOTLE (apixaban) trials;
- carotid interventions for asymptomatic patients incorporate the 10 year follow-up findings of the ACST trial;
- new recommendations on screening, identification and management of patients with obstructive sleep apnea, diagnosed both pre and post stroke;
- expansion of recommendations on smoking cessation assessment and management, including pharmacotherapy, in collaboration with the CAN-ADAPTE and C-CHANGE guideline groups; and,
- development of a TAKING ACTION FOR STROKE PREVENTION quick response guide and pocket card.

PREVENTION OF STROKE 2012 UPDATE RESOURCE PACKAGE INCLUDES:

- Prevention of Stroke Best Practice Recommendations
- Prevention of Stroke Quick Reference Guide
- Prevention of Stroke Patient Order Set
- Prevention of Stroke Educational Slide Decks
  1. Assessment of a Patient with TIA or Non-Disabling Stroke
  2. Lifestyle and Risk Factor Management To Reduce Stroke (Non-pharmacological)
  3. Pharmacotherapy for the Prevention of Stroke
- Reference Materials from:
  - Canadian Hypertension Education Program (Diagnostic Algorithm, Pharmacotherapy Table)
  - Canadian Cardiovascular Society (Atrial Fibrillation Guidelines Pocket Reference Booklet)
**STROKE PREVENTION DEFINITIONS**

**Primary prevention** is an individually based clinical approach to disease prevention, directed toward preventing the initial occurrence of a disorder in otherwise healthy individuals. Primary prevention is usually 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 are also promoted through health-oriented organizations and agencies such as the Heart and Stroke Foundation, Canadian Cardiovascular Society, Hypertension Canada, and Health Canada.

Primary prevention and the reduction of risk factor prevalence in the general population are the not main focus of the Canadian Best Practice Recommendations for Stroke Care; therefore, only selected recommendations related to primary prevention are included. A comprehensive set of recommendations in this area is being developed for inclusion in future updates. A list of existing high quality stroke prevention guidelines, including primary prevention, are provided in the reference section at the end of this chapter for further guidance (Hyperlink).

**Secondary prevention** is an individually based clinical approach aimed at reducing the risk of a recurrent vascular event in individuals who have already experienced a stroke 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.
DEVELOPMENT OF THE CANADIAN BEST PRACTICE RECOMMENDATIONS FOR STROKE CARE

For detailed methodology on the development and dissemination of the Canadian Best Practice Recommendations for Stroke Care please refer to the stroke best practices website at http://www.strokebestpractices.ca/index.php/methods/.

Acknowledgements

The Canadian Stroke Network gratefully acknowledges the task group leaders and members, the external reviewers, all of who volunteered their time and expertise to this project. We thank the Canadian Stroke Information and Evaluation Working Group for its work in updating and confirming the performance measures that accompany each recommendation. We acknowledge Corrine Davies-Schinkel for work on the systematic reviews of the literature and meeting coordination; and, we thank Marie-France Saint-Cyr and Jan Carbon for their work on the French translations.

Funding

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Citing the Prevention of Stroke Update 2012


Comments

We invite comments, suggestions, and inquiries on the development and application of the Canadian Best Practice Recommendations for Stroke Care and ongoing updates.

Please forward comments to the Canadian Stroke Network’s Performance and Standards office at bestpractices@canadianstrokenetwork.ca
**Canadian Best Practice Recommendations for Stroke Care**

**Stroke Prevention Working Group 2011-2012:**

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<thead>
<tr>
<th>Name</th>
<th>Professional Role</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coutts, Shelagh</td>
<td>Co-Chair, Stroke Neurologist, Calgary Stroke Program, Hotchkiss Brain Institute, University of Calgary</td>
<td>Alberta</td>
</tr>
<tr>
<td>Kelloway, Linda</td>
<td>Co-Chair, Best Practices Leader, Ontario Stroke Network</td>
<td>Ontario</td>
</tr>
<tr>
<td>Boulos, Mark</td>
<td>Neurology Fellow, Sunnybrook Health Sciences Centre</td>
<td>Ontario</td>
</tr>
<tr>
<td>Bradley, Douglas</td>
<td>Professor of Medicine and Director of the Division of Respirology and of the Centre for Sleep Medicine and Circadian Biology of the University of Toronto and of the Centre for Sleep Health and Research, University Health Network</td>
<td>Ontario</td>
</tr>
<tr>
<td>Ellis, Paul</td>
<td>Emergency Physician, University Health Network; Lecturer, Faculty of Medicine, University of Toronto</td>
<td>Ontario</td>
</tr>
<tr>
<td>Hudon, Mark</td>
<td>Assistant Professor of Radiology and Clinical Neurosciences, University of Calgary Diagnostic and Interventional Neuroradiology Foothills Medical Centre</td>
<td>Alberta</td>
</tr>
<tr>
<td>Kwiatkowski, Brenda</td>
<td>Nurse, Clinical Coordinator, Stroke Prevention Clinic</td>
<td>Saskatchewan</td>
</tr>
<tr>
<td>Loewen, Sherry</td>
<td>Nurse, Case Manager, Stroke Prevention Clinic</td>
<td>Manitoba</td>
</tr>
<tr>
<td>McMurtry, Michael Sean</td>
<td>Assistant Professor, University of Alberta; Canadian Cardiovascular Society liaison</td>
<td>Alberta</td>
</tr>
<tr>
<td>Murray, Brian</td>
<td>Neurologist, Director of Sunnybrook Health Sciences Centre Sleep Laboratory, University of Toronto</td>
<td>Ontario</td>
</tr>
<tr>
<td>Mysak, Tania</td>
<td>Pharmacist, Clinical Practice Manager, Pharmacy Services</td>
<td>Alberta</td>
</tr>
<tr>
<td>Nearing, Shannon</td>
<td>Nurse Practitioner, Acute Stroke Program, Queen Elizabeth II Health Sciences Centre</td>
<td>Nova Scotia</td>
</tr>
<tr>
<td>Pettersen, Jaqueline</td>
<td>Cognitive/Behavioural Stroke Neurologist; Assistant Professor, University of British Columbia</td>
<td>British Columbia</td>
</tr>
<tr>
<td>Pipe, Andrew</td>
<td>Chief, Division of Prevention and Rehabilitation, University of Ottawa Heart Institute</td>
<td>Ontario</td>
</tr>
<tr>
<td>Reid, Robert</td>
<td>Associate Director, Minto Prevention and Rehabilitation Centre, University of Ottawa Heart Institute</td>
<td>Ontario</td>
</tr>
<tr>
<td>Rioux, Annie</td>
<td>Nurse Practitioner, Stroke Prevention Clinic</td>
<td>Ontario</td>
</tr>
<tr>
<td>Ryan, Clodagh</td>
<td>Respirologist, Assistant Director of the Centre for Sleep Health and Research, University Health Network; Assistant Professor, Faculty of Medicine, University of Toronto</td>
<td>Ontario</td>
</tr>
<tr>
<td>Selby, Peter</td>
<td>Chief, Addictions Division, Ambulatory Care and Structured Treatment Program Head, Nicotine Dependence Clinic, Centre for Addiction and Mental Health Associate Professor, Departments of Family and Community Medicine, Psychiatry and Dalla Lana School of Public Health Sciences, University of Toronto</td>
<td>Ontario</td>
</tr>
<tr>
<td>Silver, Karen</td>
<td>Family Physician, Department of Family Medicine, Dalhousie University, and Memorial University</td>
<td>New Brunswick</td>
</tr>
<tr>
<td>Verreault, Steve</td>
<td>Program Director, Department of Neurology, Infant Jesus Hospital, Quebec City, University of Laval</td>
<td>Quebec</td>
</tr>
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## Canadian Best Practice Recommendations for Stroke Care

### Stroke Prevention External Reviewers 2012:

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<th><strong>LOCATION</strong></th>
</tr>
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<tbody>
<tr>
<td>Briggs, Helen</td>
<td>Drug Utilization Pharmacist, Lakeridge Health</td>
<td>Ontario</td>
</tr>
<tr>
<td>Butcher, Ken</td>
<td>Associate Professor in the Department of Medicine, Division of Adult Neurology at the University of Alberta</td>
<td>Alberta</td>
</tr>
<tr>
<td>Cote, Robert</td>
<td>Professor, Department of Neurology and Neurosurgery, McGill University</td>
<td>Quebec</td>
</tr>
<tr>
<td>Dean, Naeem</td>
<td>Clinical Professor, Faculty of Medicine, University of Alberta Director, Stroke Program, Royal Alexandra Hospital</td>
<td>Alberta</td>
</tr>
<tr>
<td>Dowlatshahi, Dariush</td>
<td>Stroke Neurologist; Associate Scientist, Neurosciences, OHRI Assistant Professor of Medicine, University of Ottawa</td>
<td>Ontario</td>
</tr>
<tr>
<td>Hanley, Patrick</td>
<td>Medical Director, Sleep Centre, Foothills Medical Centre Professor, Department of Medicine, University of Calgary</td>
<td>Alberta</td>
</tr>
<tr>
<td>Hart, Robert</td>
<td>Vascular Neurologist, Division of Neurology, Hamilton Health Sciences; Professor, Faculty of Medicine, McMaster University</td>
<td>Ontario</td>
</tr>
<tr>
<td>Johnson-Clatworthy, Linda</td>
<td>Stroke Nurse Practitioner, Markham-Stouffville Hospital</td>
<td>Ontario</td>
</tr>
<tr>
<td>McNeill, Jeanne</td>
<td>Medical Director Family Practice/Geriatrics/Palliative Care, Horizon Health Network</td>
<td>New Brunswick</td>
</tr>
<tr>
<td>Travers, Andrew</td>
<td>Provincial Medical Director, Emergency Medical Services</td>
<td>Nova Scotia</td>
</tr>
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### Canadian Best Practice Recommendations for Stroke Care

#### Best Practices and Standards Working Group

<table>
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<th><strong>MEMBER</strong></th>
<th><strong>PROFESSIONAL ROLE</strong></th>
<th><strong>LOCATION</strong></th>
</tr>
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<tbody>
<tr>
<td>Phillips, Stephan Co-Chair</td>
<td>Stroke Neurologist, Queen Elizabeth II Health Sciences Centre; Professor, Division of Neurology, Faculty of Medicine, Dalhousie University</td>
<td>Nova Scotia</td>
</tr>
<tr>
<td>Bayley, Mark Co-Chair</td>
<td>Psychiatrist; Associate Professor, University of Toronto Acquired Brain Injury, Physical Medicine &amp; Rehabilitation Toronto Rehabilitation Institute</td>
<td>Ontario</td>
</tr>
<tr>
<td>Gubitz, Gord</td>
<td>Assistant Professor, Division of Neurology Faculty of Medicine, Dalhousie University</td>
<td>Nova Scotia</td>
</tr>
<tr>
<td>Lindsay, Patrice</td>
<td>Director of Performance and Standards, Canadian Stroke Network Staff Lead, Canadian Best Practice Recommendations for Stroke Care</td>
<td>Canada</td>
</tr>
<tr>
<td>Smith, Eric</td>
<td>Stroke Neurologist &amp; Researcher Hotchkiss Brain Institute</td>
<td>Alberta</td>
</tr>
<tr>
<td>Harris, Devin</td>
<td>Clinical Associate Professor, UBC Staff, Department of Emergency Medicine, St. Paul's Hospital</td>
<td>British Columbia</td>
</tr>
<tr>
<td>Graham, Ian</td>
<td>Senior Scientist, Centre for Practice-Changing Research, The Ottawa Hospital Research Institute; Associate Professor, School of Nursing, University of Ottawa</td>
<td>Ontario</td>
</tr>
<tr>
<td>Joiner, Ian</td>
<td>Director of Stroke, Heart and Stroke Foundation of Canada</td>
<td>Canada</td>
</tr>
<tr>
<td>LeBrun, Louise- Helene</td>
<td>Stroke Neurologist, CHUM</td>
<td>Quebec</td>
</tr>
<tr>
<td>Lafferty, Katie</td>
<td>Executive Director, Canadian Stroke Network</td>
<td>Canada</td>
</tr>
<tr>
<td>Millbank, Robin</td>
<td>Manager, Professional Development and Training, Canadian Stroke Network</td>
<td>Canada</td>
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# Prevention of Stroke Best Practice Recommendations

## Best Practice Recommendation 2.1

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

1. They should receive information and counseling about possible strategies to modify their lifestyle and risk factors [Evidence Level B].
2. Referrals to appropriate specialists should be made where required to provide more comprehensive assessments and structured programs to manage risk factors [Evidence Level B].

## Lifestyle and Risk Factor Management

Lifestyle and risk factor information and counseling should be provided and include:

### 2.1.1 Healthy balanced diet:

Eating a diet high in fresh fruits, vegetables, low-fat dairy products, dietary and soluble fibre, whole grains and protein from plant sources and low in saturated fat, cholesterol (< 200 mg daily for patients at increased vascular risk) and sodium, in accordance with Canada's Food Guide to Healthy Eating [Evidence Level B].

### 2.1.2 Sodium:

Following the recommended daily sodium intake from all sources, known as the Adequate Intake. For persons 9 to 50 years, the Adequate Intake is 1500 mg. Adequate Intake decreases to 1300 mg for persons 51 to 70 years and to 1200 mg for persons over 70 years. A daily upper consumption limit of 2300 mg should not be exceeded by any age group [Evidence Level B].

### 2.1.3 Exercise:

Participating in moderate exercise such as walking (ideally brisk walking), jogging, cycling, swimming or other dynamic exercise four to seven days each week in addition to routine activities of daily living [Evidence Level A].

1. Patients should be counseled to achieve an accumulation of at least 150 minutes of moderate to vigorous activity per week, in episodes of 10 minutes or more (Refer to the CSEP Canadian Physical Activity Guidelines 2011 for additional information) [Evidence Level B].
2. Most stroke patients should be encouraged to start a regular exercise program.
   a. Supervision by a healthcare professional (physical therapist or cardiac rehab) at exercise initiation should be considered in stroke patients at risk of falls or injury, or in patients with other comorbid disease (such as cardiac disease), which may place them at higher risk of medical complications [Evidence Level C].

### 2.1.4 Weight:

Maintaining a body mass index (BMI) of 18.5 to 24.9 kg/m² or a waist circumference of <80 centimetres for women and <94 centimetres for men* [Evidence Level B]. (Note: these numbers are reflective of current research based mostly on Caucasian patients. Refer to References 24 to 31 for waist circumference values for other ethnic groups)

### 2.1.5 Alcohol consumption:

Limiting consumption to two or fewer standard drinks per day for men and one drink per day for women who are not pregnant [Evidence Level B].

### 2.1.6 Birth Control and Hormone Replacement Therapy:

Patients who are taking estrogen-containing oral contraceptives or hormone replacement therapy in the presence of stroke should have the risks and benefits of these treatments discussed with them. Management alternatives should be considered in these patients [Evidence Level B].

## Rationale

A healthy lifestyle reduces the risk of an initial stroke and the risk of a subsequent stroke for patients with a prior stroke. Hypertension is the single most important modifiable risk factor for stroke. Current research reports estimate that reducing sodium in foods would abolish high blood pressure for almost one in three Canadians. Furthermore, this 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. Regular exercise also
reduces the risk of stroke and other vascular diseases. 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.

**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.
- A public focus on arterial health for paediatric cases—such as diet, exercise, non-smoking, avoidance of drugs that increase stroke risk.
- National and international efforts to reduce sodium intake and increase public knowledge about the risks of sodium, directly targeting the food industry.
- Access to risk factor management programs (such as hypertension and smoking cessation programs) in all communities, primary healthcare settings and workplaces.
- Government actions to restrict smoking in public areas and discourage smoking through legislation and taxation initiatives.
- Coordinated efforts among stakeholders such as Heart and Stroke Foundations (national and provincial), the Canadian Stroke Network, 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 process 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 advertising the availability of educational material, effective dissemination mechanisms and follow-up.
- Educational resources, that are culturally and ethnically appropriate, are available in multiple languages and that address the needs of patients with aphasia.
- Access to healthy living programs, educational materials and healthcare professionals for persons living in rural and remote locations.

**Performance Measures**

1. Proportion of the population with major risk factors for stroke, including hypertension, obesity, history of smoking, low physical activity, hyperlipidemia, diabetes, and atrial fibrillation (core).
2. Annual occurrence rates for stroke in each province and territory by stroke type (core).
3. Stroke mortality rates across provinces and territories, including in-hospital or 30-day rate and one-year rate (core).
4. Percentage of the population who can identify the major risk factors for stroke, including hypertension, sodium intake, diet, weight, exercise, smoking and alcohol intake.
5. Percentage of people who are aware of the healthy targets for each stroke risk factor.
6. The annual readmission rate for a recurrent stroke event in patients with previous stroke or transient ischemic attack.

**Measurement notes**

- For performance measures 1, 2 and 3: self-reported data can be extracted from provincial and national health surveys.
- Performance measures 4 and 5: 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**

The literature relating to sodium consumption and health published since the release of the dietary reference intakes in 2004 includes additional 1 million cases of hypertension.

The Institute of Medicine of the National Academies established in 2004 a daily Adequate Intake for sodium of 1500 mg and a daily Tolerable Upper Intake Level of 2300 mg for healthy adults. It is well documented that a chronically high dietary sodium intake is associated with elevated blood pressure. A high intake of sodium also has direct negative effects independent of blood pressure, such as fibrosis of the heart, kidneys and arteries, including cerebral arteries. The Institute of Medicine of the National Academies established in 2004 a daily Adequate Intake for sodium of 1500 mg and a daily Tolerable Upper Intake Level of 2300 mg for healthy adults. Canadian and American governments have adopted these values for setting public health policy. The Canadian Heart Health Survey found that the average Canadian consumes about 3500 mg of sodium a day, and this high sodium intake is estimated to be responsible for a additional 1 million cases of hypertension.

The literature relating to sodium consumption and health published since the release of the dietary reference intakes in 2004 is
Weight

Observational studies have examined the relationship between body mass index (BMI) and stroke risk. Saito (2011) compared high BMIs of 27.0 to 29.9 kg/m² and BMI of >= 30.0 kg/m² to a ‘healthy’ BMI between 23.0 and 24.9 kg/m². They reported hazards ratios for increased stroke risk as 1.09 and 1.25 for men, and 1.29 and 2.16 for women. In addition, in women a weight increase of greater than 10% over the previous five years was also associated with increased stroke risk. Bazzano (2010) reported similar findings in a study of Chinese men and women, where the hazard ratios for increased stroke risk were 1.43 for persons considered overweight (BMI 25.0 to 29.9 kg/m²) and 1.72 for those who were obese with a BMI of 30 kg/m² or greater. Yatsuya (2010) found similar results (men – HR of 1.81; women – HR of 1.65), and further reported that when the analysis was adjusted for systolic blood pressure, much of the BMI risk affect was attenuated.

Some researchers have suggested that waist circumference is a preferred measurement of obesity than BMI. Dalton et al (2003) compared BMI, waist circumference (WC) and waist to hip ratio (WHR) for cardiovascular disease risk. Overall WHR showed the strongest correlations in unadjusted results, and these differences diminished when the results were adjusted for age. Women showed relationships between elevated blood pressure and both WHR and BMI. Jannsen (2004) calculated several regression models to examine the predictability of BMI and WC for hypertension, dyslipidemia and metabolic syndromes. They reported that waist circumference was a better overall predictor of obesity-related CVD risk. Yau (2011) measured waist circumference in a case-controlled observational study of independent risk factors for stroke, and reported an odds ration of 4.0 for persons with increased waist to hip ratios. Zhu et al (2004) identified formulas for calculating cardiovascular risk using a combination of BMI and WC. They determined that in while males a formula of 0.68 x BMI + 0.32 x WC was most predictive; yet in females the WC alone was a strong predictor of cardiovascular risk. Clark and colleagues (2012) caution that the current parameters for waist circumference may not be applicable to African-Americans and that research should be conducted to establish appropriate measurement standards for this population.

Physical activity

Physical activity is an important modifiable lifestyle factor that can influence both the primary and secondary prevention of stroke. Reimers and colleagues (2009) published a meta-analysis that showed physical activity reduced the risk of all stroke types (RR=0.32) for men and women combined. The results were derived from 33 prospective cohort studies and 10 case-control studies that addressed the potential effect of physical activity on stroke.

Lee and collaborators published a meta-analysis of 23 studies published between 1983 and 2002 examining the association between physical activity and stroke incidence or mortality. Eighteen cohort studies and 5 case-control studies were included for analysis. When both types of study were examined together, highly active individuals were reported as having a 27 percent 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 stroke when compared with low active individuals (RR = 0.80, p < 0.001). The benefits of high and moderate levels of activity were reported for both ischemic and hemorrhagic strokes. The meta-analysis showed increasing benefit with increasing activity, a dose–response relationship was also established. However, as Lee and collaborators pointed out, given the range of definitions of “level of physical activity” in the studies included for assessment, their analysis suffered from the lack of a single, cohesive definition of what constitutes low, moderate and high levels of activity. The question of what type or quantity of activity is required to reach a moderate level and so to benefit from a 20 percent reduction in the risk of stroke is one that needs to be investigated by means of a randomized controlled trial.

Patient adherence is important for physical activity to be effective. Jurkiewicz and colleagues (2011) found that patients that attended a rehabilitation center regularly had higher adherence to an exercise program compared to participants that had graduated and were required to do solely home-based exercise. Common factors preventing exercise that were reported by patients included: lack of motivation, musculoskeletal issues, and fatigue.

Alcohol

A meta-analysis of 35 observational studies examining the effects of alcohol consumption on stroke risk revealed a significant (p = 0.004) J-shaped relationship between the amounts of alcohol consumed per day and the risk of ischemic stroke. In that
analysis, individuals who consumed 1 to 2 drinks per day had the least risk for ischemic stroke (RR = 0.72), while those having more than 5 drinks per day had the most risk (RR = 1.69) when compared with a group of abstainers. The analysis also confirmed that alcohol consumption has a linear, dose-dependent effect on risk of hemorrhagic stroke. Heavy drinking (more than 5 drinks per day) was associated with a relative risk of hemorrhagic stroke of 2.18. Irregular and binge drinking (more than 5 drinks at one sitting) have also been associated with an increase in risk for hemorrhagic stroke.

Data from the Copenhagen City Heart Study were used to examine whether the type of alcohol consumed was related to the apparent decreased risk of ischemic stroke with moderate alcohol consumption. The overall beneficial effect of moderate alcohol consumption was confirmed; however, the benefit was seen mostly among those individuals who consumed wine. Wine drinking on a daily, weekly or monthly basis was associated with reduced risk of ischemic stroke (RR = 0.68, 0.66 and 0.88, respectively, after adjustments for age, sex, smoking, BMI, physical activity, systolic blood pressure, cholesterol, antihypertensive treatment, triglycerides, education, and diabetes). No similar effect was demonstrated among drinkers of beer or spirits. Both Kiechl and associates and Sacco reported the greatest risk reduction (RR = 0.41 and 0.40, respectively) among wine drinkers; however, this was not significantly lower than among drinkers of beer, liquor or a combination of types of alcohol.

### Oral Contraceptives, Hormone Replacement Therapy and Stroke risk in Women

Women taking oral contraceptive or hormone replacement therapy may be at an increased risk of stroke. Bath and Gray (2005) conducted a meta-analysis to assess the association between hormone replacement therapy and subsequent stroke. They identified 28 trials that included almost 40,000 patients. Their analysis found that hormone replacement therapy was associated with significant increases in 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), ischaemic stroke (OR = 1.29, 1.06 to 1.56), and a trend to more fatal stroke (OR = 1.28, 0.87 to 1.88). They also found that hormone replacement therapy was not associated with haemorrhagic stroke (OR = 1.07, 0.65 to 1.75) or transient ischaemic attack (OR = 1.02, 0.78 to 1.34). Similarly, Renoux and colleagues (2010) found that, compared to non-users, women using both low and high dose oral hormone replacement therapy had a higher rate of stroke (Rate Ratio = 1.28, 1.15-1.42); however, the use of low-dose transdermal hormone replacement therapy did not increase the risk of stroke (Rate Ratio = 0.95, 0.75-1.20).

Cole and colleagues (2007) identified women using transdermal contraceptive therapy and norgestimate-containing oral contraceptives. There was an increase in the rate of venous thromboembolism among transdermal contraceptive system users compared with norgestimate-containing oral contraceptives users (incidence rate ratio 2.2, 95% confidence interval [CI] 1.3-3.8). Stroke rate differences could not be calculated. In a large cohort study of 49, 259 Swedish women aged 30-49, found that the risk of hemorrhagic stroke was not statistically significantly raised in women who started using oral contraceptive over the age of 30 (Hazard ratio = 2.3, 0.8-6.8).
### Best Practice Recommendation 2.2  Blood Pressure Management

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

#### 2.2.1 Blood pressure assessment

All persons at risk of stroke should have their blood pressure measured routinely, ideally at each healthcare encounter, but no less than once annually [Evidence Level C].

1. 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 Canadian Hypertension Education Program. 50

2. 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 should be scheduled and completed for the assessment and diagnosis of hypertension following an initial elevated blood pressure measurement [Evidence Level C].
   b. The specific visit for assessment of hypertension should include three measurements and be conducted in accordance with the current guidelines of the Canadian Hypertension Education Program [Evidence Level C]. 50 See Figure 2.2.1

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

4. Patients with hypertension or at risk for hypertension should receive aggressive risk factor modification counseling and interventions [Evidence Level B]. Refer to recommendation 2.1 for additional information.

#### 2.2.2 Blood pressure management

Blood pressure should be managed in all patients to reach optimal control as follows:

1. For the prevention of first stroke in the general population the systolic blood pressure treatment goal is a pressure level of consistently lower than 140 mm Hg [Evidence Level B]. The diastolic blood pressure treatment goal is a pressure consistently lower than 90 mm Hg [Evidence Level A].

2. 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].

3. 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 B] and diastolic blood pressure targets consistently lower than 80 mm Hg [Evidence Level A].

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

5. For recommendations on specific agents and sequence of agents for the secondary prevention of stroke, refer to the Canadian Hypertension Education Program treatment guidelines [Evidence Level C]. 50 Refer to Table 2.2.

6. 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 recommendation 3.3 for blood pressure management during the acute phase of stroke (0 – 72 hours).

### 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.\textsuperscript{50, 51} Each 1 mm Hg increase in blood pressure increases the risk of poor late-life cognitive function by approximately one percent.\textsuperscript{52,53} 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.\textsuperscript{54} 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 for healthcare providers across the continuum of care on hypertension diagnosis and management for adults and children.
- Increased programs for patients and families on home monitoring of blood pressure and blood pressure self-management programs.

**Performance Measures**

1. Proportion of persons at risk for stroke who had their blood pressure measured at their last healthcare encounter.
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. Proportion of the population who report having hypertension.
5. Percentage of the population with known hypertension who are on blood pressure lowering therapy.
6. 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).
7. Proportion of stroke and transient ischemic attack patients who have received a prescription for blood pressure lowering agents on discharge from acute care.
8. 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 4: 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 5 and 6: data may be available through audit of primary care physician 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 and 8: 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 physician 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.\textsuperscript{104}
Implementation Resources and Knowledge Transfer Tools

- Canadian Hypertension Education Program: http://www.hypertension.ca/chep-recommendations
- Home monitoring and other Canadian Hypertension Education Program resources: http://hypertension.ca/measuring-blood-pressure
- Aboriginal Hypertension Management Resources: http://www.heartandstroke.on.ca/site/c.pv13leNWJwe/b.5339657/k.9CEB/HCP__Aboriginal_Hypertension_Management_Program_Resources.htm

Summary of the Evidence

**LINK to Evidence Tables for Blood Pressure Management**

Hypertension is a major problem in nearly all countries around the world, including Canada, and it is the most important modifiable risk factor for stroke. The INTERSTROKE study is an ongoing case-controlled study of the contribution of specific risk factors to the burden of stroke across 22 countries. The first report from this study, based on 3,000 stroke cases and 3,000 controls, identified five risk factors which account for more than 85 percent of the risk for stroke, including hypertension, current smoking, abdominal obesity, diet, and physical activity. Among these risk factors, hypertension was the most significant risk factor for stroke and contributed to 34.6 percent of the population-attributed risk (PAR), and this rose to 52 percent when measured blood pressures of greater than 160/90 mm Hg were added to the model. When these results were compared to a similar study conducted for heart disease, hypertension was found to have a more significant impact on stroke than on heart disease. The study further noted that “blood pressure is the most amenable to change in low-income settings because screening programs need modest equipment and little specialized expertise. Additionally, blood pressure is readily reduced by inexpensive generic drugs and non-pharmacological approaches (e.g., salt reduction)” (page 9).

Du and associates reported that some 20–30 percent of adult populations are affected with high blood pressure, as are over 60 percent of people 65 years and older and about 70 percent of stroke patients. Hypertension is quantitatively the largest single risk factor for premature death and disability, because of the large number of people afflicted and the consequences of uncontrolled hypertension. Hypertension is closely associated with the risk of total mortality and the risk of all types of stroke, coronary artery disease, diabetes and renal disease. No other modifiable factor has been identified that contributes more to the development of stroke than hypertension. The authors further emphasized that hypertension should not be regarded so much as a disease but more as one of the treatable or reversible risk factors for premature death due to arterial disease. At least three-quarters of strokes in hypertensive patients are preventable by treatment of elevated blood pressure. However, strokes are caused not by a single risk factor such as hypertension but by the interaction of multiple risk factors, some having a stronger independent relationship with risk of stroke than others. The probability of stroke in an individual depends on the presence and level of other risk factors.

The National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure has defined normal blood pressure as less than 120/80 mm Hg. A continuous and linear relationship between blood pressure and risk of stroke has been reported, which holds even in individuals with normal blood pressure. Lewington found that an increase of 20 mm Hg in systolic and 10 mm Hg in diastolic blood pressure can lead to a two-fold increase in stroke mortality in persons aged 40 – 69. Weber reported that the high sensitivity of the relationship between blood pressure and stroke risk is now more fully realized. Single studies do not always have the power to identify the impact that blood pressure changes of only a few millimetres of mercury have on risk. However, strokes are caused not by a single risk factor such as hypertension but by the interaction of multiple risk factors, some having a stronger independent relationship with risk of stroke than others. The probability of stroke in an individual depends on the presence and level of other risk factors.

A collaborative meta-analysis was conducted to assess the age-specific relevance of blood pressure to cause-specific mortality. Combining 61 prospective observational studies of blood pressure and vascular mortality, each difference of 20 mm Hg in systolic blood pressure (or, approximately equivalently, 10 mm Hg in usual diastolic blood pressure) was associated with more than a two-fold difference in the stroke death rate, 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.

Lee (2011) reported that patients with a systolic BP of 120 to 129 mmHg have a relative risk of stroke of 1.22, and this increases to a relative risk of 1.79 when systolic blood pressure is between 130 and 139 mmHg. These increased risk patterns have been measured for recurrent stroke and appear similar. Obviaele (2011) reported a linear relationship between systolic blood pressure and risk of recurrent stroke, with the high SBP group (SBP 140-150 mmHg) (AHR, 1.23; 95% CI, 1.07-1.41), and in the very high SBP group (SBP > 150 mmHg) (AHR, 2.08; 95% CI, 1.63-2.37).
A Cochrane meta-analysis by Musini and associates also examined the effects of age and blood pressure lowering on overall mortality, cardiovascular mortality and morbidity and withdrawal due to adverse effects in people 60 years and older with mild to moderate systolic or diastolic hypertension.63 Fifteen trials (24,055 subjects ≥ 60 years) with moderate to severe hypertension were included which mostly evaluated first-line thiazide diuretic therapy for a mean duration of treatment of 4.5 years. Treatment reduced total mortality, RR 0.90 (0.84, 0.97); event rates per 1000 participants reduced from 116 to 104. Treatment also reduced total cardiovascular morbidity and mortality, RR 0.72 (0.68, 0.77); event rates per 1000 participants reduced from 149 to 106. 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 RR 0.75 [0.65, 0.87] however, there was no reduction in total mortality, RR 1.01 [0.90, 1.13]. Withdrawals due to adverse effects were increased with treatment, RR 1.71 [1.45, 2.00]. The authors concluded that treating healthy persons (60 years or older) with moderate to severe systolic and/or diastolic hypertension reduces all-cause mortality and cardiovascular morbidity and mortality. The decrease in all-cause mortality was limited to persons 60 to 80 years of age.

The relationship between blood pressure and cardiovascular risk is “continuous, consistent, and independent of other risk factors. The American Heart Association guidelines for the primary prevention of ischemic stroke report that the higher the blood pressure, the greater the stroke risk.64 The working group acknowledged the benefit of treatment of hypertension for the primary prevention of stroke and concluded that the reduction of blood pressure is generally more important than the agent used to aid in this goal.

Hypertensive patients with a history of cerebral vascular disease are at particularly high risk of stroke recurrence. Gueyffier and associates performed a meta-analysis using all available randomized controlled clinical trials assessing the effect of blood pressure lowering drugs on clinical outcomes (recurrence of stroke, coronary events, cause-specific and overall mortality) in patients with prior stroke or transient ischemic attack.65 Nine trials that included a total of 6752 patients were identified, and it was found that the recurrence of stroke, fatal and nonfatal, was significantly reduced in treatment groups compared with control groups consistently across the different sources of data (RR = 0.72, 95% CI 0.61–0.85). There was no evidence that this intervention induced serious adverse effects.

For several reasons, categorizing patients as “hypertensive” or “normotensive” based on an arbitrary blood pressure threshold may not be helpful with respect to secondary stroke prevention. First, the relationship between blood pressure and stroke is continuous and graded, with no evidence of a lower blood pressure threshold for stroke risk. Second, several controlled trials have demonstrated that blood pressure reduction benefits patients who would not normally be designated as hypertensive (Heart Outcomes Prevention Evaluation [HOPE],66 PROGRESS67). Blood pressure lowering therapy reduces the risk of vascular events across a wide spectrum of initial blood pressures.66–68

Angiotensin receptor blockers have demonstrated efficacy for the prevention of stroke in both the primary and secondary prevention settings. Three recently completed trials of angiotensin receptor blockers were the Losartan Intervention For Endpoint Reduction Study (LIFE),69 the Acute Candesartan Cilexetil Therapy in Stroke Survivors Study (ACCESS pilot study),70 and the Study on Cognition and Prognosis in the Elderly (SCOPE).71 All three trials demonstrated consistent relative risk reductions for stroke in the range of 24 percent to 34 percent, despite the enrolment of different patient populations, the use of varying angiotensin receptor blockers and differing interventions in the control group (placebo-based or conventional therapy).

The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) compared the ACE inhibitor ramipril, the angiotensin-receptor blocker telmisartan and the combination of the two drugs in patients with vascular disease or high-risk diabetes.72 Patients underwent double-blind randomization, with 8576 assigned to receive 10 mg of ramipril per day, 8542 assigned to receive 80 mg of telmisartan per day and 8502 assigned to receive both drugs (combination therapy). The primary composite outcome was death from cardiovascular causes, myocardial infarction, stroke or hospitalization for heart failure. The researchers found 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 increase in benefit.

Studies of hypertension management in the very elderly have emerged in the past few years.73,74 The HYVET study involving 3845 patients examined the benefit of antihypertensive treatment for hypertensive patients who were 80 years or older.75 Patients were randomly assigned to receive either antihypertensive therapy or matching placebo. The results showed that lowering mean blood pressure by 15.0/6.1 mm Hg was associated with a 30 percent reduction in the rate of fatal or nonfatal stroke (95% CI −1% to 51%, p = 0.06), a 39 percent reduction in the rate of death from stroke (95% CI 1% to 62%, p = 0.05), a 21 percent reduction in the rate of death from all causes (95% CI 4% to 35%, p = 0.02) and a 23 percent reduction in the rate of death from cardiovascular causes (95% CI −1% to 40%, p = 0.06). Fewer serious adverse events were reported in the active treatment group (358 vs. 448 in the placebo group, p = 0.001). The authors concluded that antihypertensive treatment in patients 80 years of age or older was beneficial.

An open-label active treatment extension of the HYVET study included 1682 patients both from the original treatment and the placebo group (Beckett et al 2012).74 All patients followed the medication regime as the original trial (indapamide SR 1.5 mg plus perindopril 2-4 mg if required), had the same target blood pressure levels of less than 150/80 mm Hg, and measured the same end point of stroke, all cause mortality, cardiovascular mortality, and other cardiovascular events. No differences were found between the groups, demonstrating that both early and long-term antihypertensive therapies are beneficial to elderly patients.
Launer and coworkers assessed the long-term relationship of midlife blood pressure levels to late-life cognitive function in the surviving cohort members of the prospective Honolulu Heart Program. The subjects were 3735 Japanese American men living in Hawaii either in the community or in institutions, with an average age of 78 years at the fourth examination. Cognitive function, measured by the 100-point Cognitive Abilities Screening Instrument, was categorized as good (reference category, with score of 92 to 100), intermediate (score < 92 to 82) and poor (score < 82). Midlife systolic blood pressure and diastolic blood pressure values were measured in 1965, 1968 and 1971. A respondent was classified into one of the following categories if 2 of 3 measurements fell into the following groups: for systolic blood pressure, < 110, 110 to 139, 140 to 159 and ≥ 160 mm Hg; and for diastolic blood pressure, < 80, 80 to 89, 90 to 94 and 95 mm Hg. The risk for intermediate and poor cognitive function increased progressively with increasing level of midlife systolic blood pressure category (p for trend < 0.03 and < 0.001, respectively) when controlled for age and education. For every 10 mm Hg increase in systolic blood pressure there was an increase in risk for intermediate cognitive function of 7 percent (95% CI 3%–11%) and for poor cognitive function of 9 percent (95% CI 3%–16%). The level of cognitive function was not associated with midlife diastolic blood pressure. The authors concluded that early control of systolic blood pressure levels may reduce the risk for cognitive impairment in old age.
Figure 2.2.1 Canadian Hypertension Education Program (2012)

Figure 1. The Expedited Assessment and Diagnosis of Patients With Hypertension:

Focus on Validated Technologies for Blood Pressure Assessment*

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### Table 2.2.1 CHEP Hypertension Pharmacomangement Table (2012)

**Considerations in the Individualization of Antihypertensive Therapy**

<table>
<thead>
<tr>
<th>Hypertension Without Other Compelling Indications</th>
<th>Target &lt; 140/90 mmHg</th>
<th>Second-line Therapy</th>
<th>Notes and/or Cautions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diastolic +/- Systolic Hypertension</strong></td>
<td></td>
<td>Combinations of first-line drugs</td>
<td>Not recommended for monotherapy. Alpha blockers, Beta-blockers in those &gt; 60 years of age. ACE inhibitors in blacks. Hypokalemia should be avoided in those prescribed diuretics monotherapy. ACE inhibitors, ARBs and direct renin inhibitors are potential teratogens, and caution is required if prescribing to women of child-bearing potential. Combination of an ACE inhibitor with an ARB is not recommended.</td>
</tr>
<tr>
<td>isolated systolic hypertension without other compelling indications</td>
<td></td>
<td>Combinations of first-line drugs</td>
<td>Same as diastolic +/- systolic hypertension</td>
</tr>
<tr>
<td><strong>Diabetes Mellitus</strong></td>
<td>Target &lt; 130/80 mmHg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus with microalbuminuria*, cardiovascular disease, renal disease or additional cardiovascular risk factors</td>
<td>ACE inhibitors or ARBs</td>
<td>Addition of dihydropyridine CCB is preferred over thiazide</td>
<td>A loop diuretic could be considered in hypertensive CKD patients with extracellular fluid volume overload</td>
</tr>
<tr>
<td>Diabetes mellitus not included in the above category</td>
<td>ACE inhibitors, ARBs, dihydropyridine CCBs or thiazide diuretics</td>
<td>Combination of first-line drugs. If combination with ACE inhibitor is being considered, a dihydropyridine CCB is preferable to thiazide diuretics.</td>
<td>Normal albumin to creatinine ratio (ACR) &lt;2.0 mg/mmol in men and &lt;2.9 mg/mmol in women. Combination of an ACE inhibitor with an ARB is specifically not recommended.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiovascular Disease</th>
<th>Target &lt; 140/90 mmHg</th>
<th>Second-line Therapy</th>
<th>Notes and/or Cautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary artery disease**</td>
<td>ACE inhibitors or ARBs (except in low-risk patients; beta blockers for patients with stable angina)</td>
<td>Long-acting CCBs. When combination therapy is being used for high risk patients, an ACE inhibitor/dihydropyridine CCB is preferred</td>
<td>Avoid short-acting nitrates. Combination of an ACE inhibitor with an ARB is specifically not recommended.</td>
</tr>
<tr>
<td>Recent myocardial infarction</td>
<td>Beta-blockers and ACE inhibitors (ARBs if ACE inhibitor intolerant)</td>
<td>Long-acting CCBs if beta blocker contraindicated or not effective</td>
<td>Non-dihydropyridine CCBs should not be used with concomitant heart failure.</td>
</tr>
<tr>
<td>Heart failure</td>
<td>ACE inhibitors (ARBs if ACE inhibitor-intolerant) and beta-blockers. Aldosterone antagonists (mineralocorticoid receptor antagonists) may be added for patients with a recent cardiovascular hospitalization, acute myocardial infarction, elevated BNP or NT-proBNP level, or NYHA Class II to IV symptoms.</td>
<td>ACE inhibitor and ARB combined. Hydralazine/ isosorbide dinitrate combination if ACE inhibitor and ARB contraindicated or not tolerated. Thiazide or loop diuretics are recommended as additive therapy. Dihydropyridine CCB.</td>
<td>Titrate doses of ACE inhibitors and ARBs to those used in clinical trials. Carefully monitor potassium and renal function if combining an ACE inhibitor, ARB and/or aldosterone antagonist.</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>ACE inhibitor, ARB, long acting CCB or thiazide diuretics.</td>
<td>Combination of additional agents</td>
<td>Hydralazine and minoxidil should not be used.</td>
</tr>
<tr>
<td>Past stroke or TIA</td>
<td>ACE inhibitor/diuretic combinations</td>
<td>Combinations of additional agents</td>
<td>Treatment of hypertension should not be routinely undertaken in acute stroke unless extreme BP elevation. Combination of an ACE-inhibitor with an ARB is not recommended.</td>
</tr>
<tr>
<td>Non-diabetic chronic kidney disease</td>
<td>Target &lt; 140/90 mmHg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-diabetic chronic kidney disease with proteinuria</td>
<td>ACE inhibitors (ARBs if ACEI- intolerant) if there is proteinuria</td>
<td>Combinations of additional agents.</td>
<td>Carefully monitor renal function and potassium for those on an ACE inhibitor or ARB. Combinations of an ACE-inhibitor and ARB are not recommended in patients without proteinuria.</td>
</tr>
<tr>
<td>Renovascular disease</td>
<td>Does not affect initial treatment recommendations</td>
<td>Combinations of additional agents</td>
<td>Avoid ACE inhibitors or ARB if bilateral renal artery stenosis or unilateral disease with solitary kidney</td>
</tr>
</tbody>
</table>

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Best Practice Recommendation 2.3 Lipid Management

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

2.3.1 Lipid assessment

i. Fasting lipid levels (total cholesterol, total triglycerides, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol) should be measured on all patients presenting with stroke or TIA [Evidence Level C].

ii. For management of dyslipidemia in the primary prevention of cardiovascular events, including stroke, refer to the current Canadian Cardiovascular Society Dyslipidemia clinical practice guidelines.78

2.3.2 Lipid management

i. A statin drug should be prescribed for primary prevention of cardiovascular events, including stroke, to most patients with high global cardiovascular risk [Evidence Level A].

ii. A statin drug should be considered for primary prevention of cardiovascular events, including stroke, for those patients at intermediate cardiovascular risk [Evidence Level B]. Refer to Canadian Cardiovascular Guidelines for Dyslipidemia 2012 for additional information.

iii. A statin drug should be prescribed as secondary prevention to most patients who have had an ischemic stroke or transient ischemic attack in order to achieve an LDL cholesterol of less than 2.0 mmol/L, or a 50% reduction in LDL cholesterol from baseline [Evidence Level B].

iv. Patients with ischemic stroke or transient ischemic attack should be managed with aggressive therapeutic lifestyle changes, including dietary modification, as part of a comprehensive approach to lower risk of first or recurrent stroke [Evidence Level A].

v. Statin therapy is not indicated for prevention of intracerebral hemorrhage. For intracerebral hemorrhage patients who have a clear concomitant indication for cholesterol lowering treatment, statin therapy should be individualized and should take into account the patient’s overall thrombotic risk as well as the possibility of increased risk of intracerebral hemorrhage on statin therapy [Evidence Level B].

vi. Statin therapy has not been well studied in certain sub-populations of stroke patients (for example, patients over 80 years of age, patients with cardioembolic stroke, arterial dissection). Decisions for prescribing should be based on current health status, comorbidities and other indicators of systemic vascular disease (such as coronary artery disease, peripheral vascular disease, and renal vascular disease][Evidence Level C].

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.77

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 for healthcare providers across the continuum of care on dyslipidemia diagnosis and management.
- Continued alignment with recommendations and guidelines developed by the Canadian Cardiovascular Society Dyslipidemia group.

Performance Measures

1. 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 physician.
2. Proportion of the population who report that they have elevated lipid levels, especially low-density lipoprotein.
3. Proportion of stroke patients with a low-density lipoprotein cholesterol between 1.8 and 2.5 mmol/L at three months following the stroke event.
4. Proportion of stroke patients who have lipid levels completed as part of initial comprehensive assessment.
5. Proportion of stroke patients who have lipid levels completed as part of initial comprehensive assessment with elevated lipid levels that require and receive treatment.

Measurement Notes

- Performance measures 1 and 2: Data may be available through the Canadian Community Health Survey.
- Performance measure 2: Data sources may include physician order sheets, physicians’ and nurses’ notes, discharge summaries, or copies of prescriptions given to patients.
- Performance measure 3: Blood values should be taken from official laboratory reports where possible.
- 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

- Canadian Cardiovascular Society Dyslipidemia Recommendations: [link]
- Heart and Stroke Foundation of Canada: [link]
- Dieticians of Canada: [link]
- Framingham Cardiovascular Risk Calculator: [link]
- Cholesterol Levels Calculator: [link]
- National Heart, Lung and Blood Institute Patient Educational Materials: [link]
- Live Strong: [link]

Summary of the Evidence

**LINK to Evidence Tables for Lipid Management**

The causal relationship between dyslipidemia and atherosclerosis is well documented. Screening and appropriate management of dyslipidemia by healthcare providers is imperative in both primary and secondary prevention of coronary artery disease, peripheral vascular disease and stroke. The 2009 update of the Canadian dyslipidemia guidelines provides a detailed description of the current recommended treatment levels and management modalities for dyslipidemia. They emphasize a need to balance lifestyle and risk factor modifications through behaviors change with pharmacological intervention to maximize treatment and improve outcomes for cardiovascular disease and stroke.
Several systematic reviews of lipid-lowering therapies have affirmed the following points: (1) the relative reduction in stroke risk is on the order of 25–30 percent, (2) ischemic stroke is reduced, with little effect on hemorrhagic stroke and (3) the relative reduction in stroke events is constant irrespective of the baseline risk of stroke. The latter indicates that a greater absolute benefit may accrue from treating patients with a history of stroke or transient ischemic attack, who have a markedly higher baseline risk of recurrent cerebrovascular events.79,84

O’Regan and collaborators conducted a comprehensive review of randomized trials evaluating statin therapy for stroke prevention.85 Data were pooled using a random-effects model, and meta-regression techniques were employed. Following a thorough search, 42 trials assessing statin therapy for all-stroke prevention (n = 121,285) were included, resulting in a pooled RR of 0.84 (95% CI 0.79–0.91). The pooled relative risk of statin therapy for all-cause mortality (n = 116,080) was 0.88 (95% CI 0.83–0.93). Each unit increase in LDL resulted in a 0.3 percent increased RR of death (p = 0.02). Seventeen trials evaluated the effect of statins on cardiovascular death (n = 57,699, RR 0.81, 95% CI 0.74–0.90), and 11 evaluated non-hemorrhagic cerebrovascular events (n = 58,604, RR 0.81, 95% CI 0.69–0.94). Eleven trials reported hemorrhagic stroke incidence (total n = 54,334, RR 0.94, 95% CI 0.69–1.30), and 21 trials reported on fatal strokes (total n = 82,278, RR 0.99, 95% CI 0.80–1.21).86 Only one trial reported on statin therapy for secondary prevention. Statin therapy provides high levels of protection for all-cause mortality and non-hemorrhagic strokes, reinforcing the need to consider prolonged statin treatment for patients at high risk of major vascular events, but a need for caution remains for patients at risk of bleeds. A large meta-analysis of various lipid-lowering therapies (including statins, fibrates, niacin, bile acid sequestrants and diet) found that only statins reduced the risk of stroke, with a risk reduction of 26 percent (95% CI 14%–36%) for secondary prevention.87 Non-statin drug therapy (with 32,550 subjects studied, of whom 73% were randomized in trials employing fibrates) was associated with a nonsignificant risk reduction of seven percent (RR 0.93, 95% CI 0.79–1.08).

The Heart Protection Study contributed a substantial amount of information about the role of statin therapy in persons at high risk of serious vascular events.82 This study randomized 20,536 patients with a total serum cholesterol of > 3.4 mmol/L to simvastatin or placebo for a mean duration of five years. The inclusion criteria were any of the following: coronary artery disease, cerebrovascular disease, peripheral vascular disease, diabetes or patients over 65 years with hypertension. The study showed that simvastatin 40 mg once daily rapidly produced a definite and substantial reduction in ischemic stroke (relative risk reduction 25 percent; 95% CI 15%–44%), irrespective of the patient’s age, sex or blood lipid concentrations when treatment was initiated.82 It also demonstrated that statin therapy reduced the risk of major vascular events among people who have previously had a stroke or other cerebrovascular event, even if they did not already have manifest coronary disease. In addition, there was a highly significant reduction in the simvastatin arm in the frequency of carotid endarterectomy and angioplasty. These benefits were evident in every subgroup tested: patients who had or did not have coronary artery disease; those with cerebrovascular disease, peripheral vascular disease or diabetes; men or women; those over or under 75 years at entry; and those whose LDL cholesterol was over or under 2.6 mmol/L. Treatment benefits were independent of the baseline cholesterol level. The results of the Heart Protection Study imply that the initiation of statin therapy should be based more on the assessment of a patient’s absolute risk of cardiovascular disease, rather than just the baseline LDL cholesterol concentration.

The Stroke Prevention by Aggressive Reduction in Cholesterol Levels trial (SPARCL) randomly assigned 4731 patients who had had a stroke or transient ischemic attack within one to six months before study entry, had LDL levels of 2.6 to 4.9 mmol/L and had no known coronary artery disease to double-blind treatment with atorvastatin 80 mg once daily or placebo.83 The mean LDL level during the trial was 1.9 mmol/L among patients receiving atorvastatin and 3.3 mmol/L in the placebo group. The 5-year absolute reduction in risk of any stroke was 2.2 percent; relative risk reduction of 16%, adjusted hazard ratio (HR) 0.84 (95% CI 0.71–0.99; p = 0.03). The reduction in ischemic stroke (HR 0.78, 95% CI 0.66–0.94) should be weighed against the statistically significant increase in hemorrhagic stroke (HR 1.66, 95% CI 1.08 – 2.55). The five-year absolute reduction in risk of major cerebrovascular events was 3.5 percent (HR 0.90, 95% CI 0.69–0.92; p = 0.002). The statistically significant increase in hemorrhagic stroke, not seen in other statin trials, remains unexplained.83

In the second Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL2) study, atorvastatin 80 mg/day reduced the risk of stroke in patients with recent stroke or transient ischemic attack.84 This overall benefit included an increase in the numbers of treated patients having hemorrhagic stroke (n = 55 for active treatment v. n = 33 for placebo), prompting investigators to further explore the relationships between hemorrhage risk and treatment, baseline patient characteristics, most recent blood pressure and most recent LDL cholesterol levels before the hemorrhage. Of 4731 patients, two percent had hemorrhagic strokes as entry events.85 In addition to atorvastatin treatment (HR 1.68, 95% CI 1.09–2.59; p = 0.02), Cox multivariable regression showed that hemorrhagic stroke risk was higher in those having a hemorrhagic stroke as the entry event (HR 5.65, 95% CI 2.82–11.30; p < 0.001), in men (HR 1.79, 95% CI 1.13–2.84; p = 0.01) and with age (10-yr increments, HR 1.42, 95% CI 1.16–1.74; p < 0.001). There were no statistical interactions between these factors and treatment. Multivariable analyses also found that having stage 2 (JNC-7) hypertension at the last study visit before a hemorrhagic stroke increased risk (HR 6.19, 95% CI 1.47–26.11; p = 0.01), but there was no effect of most recent LDL cholesterol level in those treated with atorvastatin.
Best Practice Recommendation 2.4 Diabetes Management

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

2.4.1 Diabetes assessment
i. For patients with diabetes and either ischemic stroke or transient ischemic attack, glycated hemoglobin (HbA1C) should be measured as part of a comprehensive stroke assessment [Evidence Level B].
ii. In all patients with stroke or TIA, fasting lipid levels (total cholesterol, high-density lipoprotein cholesterol, total glycerides and calculated low-density lipoprotein cholesterol) should be measured at the time of diagnosis and at appropriate intervals if therapy initiated [Evidence Level C].
iii. Blood pressure should be measured at every diabetes visit in patients with stroke or at risk of stroke [Evidence Level C].

2.4.2 Diabetes management
i. Glycemic targets must be individualized; however, therapy in most patients with type 1 or type 2 diabetes and stroke or TIA should be treated to achieve a glycated hemoglobin (HbA1C) level ≤7.0 percent to reduce the risk of microvascular complications [Evidence Level A] and, in individuals with type 1 diabetes, macrovascular complications [Evidence Level C].
ii. To achieve an HbA1C ≤7.0%, 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 HbA1C 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, can be considered [Evidence Level C].
iv. 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 A].
v. Unless contraindicated, low dose acetylsalicylic acid therapy (81 to 325 mg/day) is recommended in all patients with diabetes with evidence of cardiovascular disease such as stroke [Evidence Level A].

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 the Canadian Diabetes Association.

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

### Measurement Notes
- 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.
- Performance measure 2: Rates may be obtained for Canada from the Public Health Agency of Canada Diabetes Surveillance database.

### Implementation Resources and Knowledge Transfer Tools

### Summary of the Evidence

#### LINK to Evidence Tables for Diabetes Management in Stroke and TIA Patients

Diabetes is an important modifiable risk factor for a first ischemic stroke. In a review of stroke and diabetes, Idris and colleagues stated that the combination of diabetes and stroke is a major cause of morbidity and mortality worldwide. Evidence from large clinical trials performed in patients with diabetes supports the need for aggressive and early intervention to target patients’ cardiovascular risks to prevent the onset, recurrence and progression of acute stroke. They describe the epidemiology of diabetes and stroke, and report an estimate that the risk of stroke is increased 1.5- to three-fold for patients with diabetes. Diabetes also doubles the risk of stroke recurrence, and stroke outcomes are significantly worse among patients with diabetes, with increased hospital and long-term stroke mortality, more residual neurologic and functional disability and longer hospital stays. From a clinical perspective, diabetes increases the risk of ischemic stroke more than hemorrhagic stroke, resulting in a greater ischemic to hemorrhagic stroke ratio in people with diabetes compared with the general population. Idris and colleagues further reported that although strokes in patients with diabetes are associated with a worse outcome, there is no evidence to suggest that diabetes induces a larger area of cerebral infarction.

The high stroke risk in diabetes may be due to the complex interplay between the various hemodynamic and metabolic components of the diabetes syndrome. Other than the many recognized risk factors associated with acute stroke (e.g., hypertension, dyslipidemia and atrial fibrillation), specific risk factors attributable to diabetes have also been reported. Components of the metabolic syndrome such as insulin resistance, central obesity, impaired glucose tolerance and hyperinsulinemia, both individually and collectively, are associated with an excess risk of stroke disease. Many diabetes patients exhibit metabolic syndrome and these additional risk factors, such as raised hypertension and cholesterol, multiply the overall risk. Reducing these risk factors to target levels is essential and requires a multifactor approach. Lifestyle changes, tight glycemic control, antiplatelet drugs (ASA) and control of lipid levels, (e.g., using statins), can all have significant 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 ACE inhibitors as first-line treatment in patients with diabetes.

Karapanayiotides and collaborators reported that the Framingham Study found a 2.5-fold incidence of ischemic stroke in diabetic men and a 3.6-fold incidence in diabetic women. In the largest case–control study with adjustment for multiple known risk factors, the risk of ischemic stroke for diabetic individuals was increased 2.3-fold. Two other large studies reported similar findings with odds ratios (ORs) of 2.12 and 2.47. However, it is difficult to determine the level of association between diabetes and ischemic stroke, as diabetes is also associated with a two-fold higher incidence of hypertension and cardiac disease and with an increased incidence of asymptomatic carotid artery disease and hyperlipidemia. Karapanayiotides and collaborators concluded that other risk factors for stroke such as hypertension, hypercholesterolemia, cardiac ischemic disease and vascular claudication are significantly more frequent in diabetic individuals, confirming that diabetic patients have high cerebral and cardiovascular risk.

Lehto and coworkers conducted a seven-year follow-up study on diabetic patients and nondiabetic controls to assess risk for stroke. They found diabetic men had a two- to three-fold higher risk, and diabetic women a five-fold higher risk for stroke than corresponding nondiabetic subjects (men: OR 2.4, 95% CI 1.2–4.9 in East Finland; OR 3.3, 95% CI 1.6–6.9 in West Finland; women: OR 5.5, 95% CI 2.4–12.9 in East Finland; OR 5.4, 95% CI 2.3–12.6 in West Finland). Ischemic stroke was the most common cause of stroke in nondiabetic subjects and type 2 diabetes patients in both areas. High fasting plasma glucose was a risk factor for stroke even after adjustment for other variables. In addition to fasting plasma glucose, glycemic control was also assessed by HbA1c, which reflects hyperglycemia during the preceding two months. There was a dose-response relationship between HbA1c and risk of stroke. The duration of diabetes was also an important risk factor for stroke events in type 2 subjects. In addition, low levels of HDL cholesterol (less than 0.90 mmol/L), high levels of total triglyceride (more than 2.30...
mmol/L) and the presence of hypertension were associated with a 2-fold increase in the risk of stroke mortality or morbidity.

The Treating to New Targets study showed that intensive lipid-lowering therapy with atorvastatin 80 mg/day provides significant clinical benefit beyond that afforded by atorvastatin 10 mg/day in patients with stable coronary artery disease. A total of 1501 patients with diabetes and coronary artery disease, with LDL cholesterol levels of < 3.36 mmol/L, were randomized to double-blind therapy with either atorvastatin 10 (n = 753) or 80 (n = 748) mg/day. Patients were followed for a median of 4.9 years. The primary end point was the time to first major cardiovascular event, defined as death from coronary heart disease, nonfatal non–procedure related myocardial infarction, resuscitated cardiac arrest, or fatal or nonfatal stroke. The results found end-of-treatment mean LDL cholesterol levels were 2.55 mmol/L with atorvastatin 10 mg and 1.99 mmol/L with atorvastatin 80 mg. A primary event occurred in 135 patients (17.9%) receiving atorvastatin 10 mg, compared with 103 patients (13.8%) receiving atorvastatin 80 mg (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 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 and persistent elevations in liver enzymes. The researchers concluded that among patients with clinically evident coronary artery disease and diabetes, intensive therapy with atorvastatin 80 mg significantly reduced the rate of major cardiovascular events by 25 percent compared with atorvastatin 10 mg.

The Action to Control Cardiovascular Risk in Diabetes Study (ACCORD) investigators assessed whether intensive therapy to target normal HbA1c levels would reduce cardiovascular events in patients with type 2 diabetes who had either established cardiovascular disease or additional cardiovascular risk factors. Patients (n = 10 251) with a median HbA1c level of 8.1 percent were randomly assigned to receive intensive therapy (targeting an HbA1c level below 6.0 percent) or standard therapy (targeting a level from 7.0 percent to 7.9 percent). The finding of higher mortality in the intensive-therapy group led to a discontinuation of intensive therapy after a mean of 3.5 years of follow-up. During follow-up, the primary outcome occurred in 352 patients in the intensive-therapy group, as compared with 371 in the standard-therapy group (HR 0.90, 95% CI 0.78–1.04; p = 0.16). At the same time, 257 patients in the intensive-therapy group died, as compared with 203 patients in the standard therapy group (HR 1.22, 95% CI 1.01–1.46; p = 0.04). These findings identify a previously unrecognized harm of intensive glucose lowering in high-risk patients with type 2 diabetes.

The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial 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 glycated hemoglobin 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).
Best Practice Recommendation 2.5

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 (81 mg to 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].
   - For adult patients on acetylsalicylic acid, most patients should be on a maintenance dose of 81 mg/day unless other indications are present which may suggest a higher dose is required [Evidence Level A].

ii. In children with stroke the usual maintenance dosage of acetylsalicylic acid is 1 to 5 mg/kg per day for the prevention of recurrent stroke [Evidence Level B]. The usual maximum dose is 81 mg/day.

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

iv. Short-term concurrent use of acetylsalicylic acid and clopidogrel (up to 90 days) has not shown an increased risk of bleeding [Evidence Level B]; however, longer-term use is not recommended for secondary stroke prevention, unless there is an alternate indication (e.g., drug-eluting carotid artery stent requiring dual antiplatelet therapy), due to an increased risk of bruising and bleeding [Evidence Level A].

v. At the present time, there is not enough evidence to guide management if a patient has a stroke while on a specific antiplatelet agent. Some clinicians may choose to switch to an alternate antiplatelet agent. In all cases other vascular risk factors should be aggressively managed [Evidence Level C].

Refer to recommendation 2.6 for additional information on combination therapy for patients with stroke and atrial fibrillation.

Rationale

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

System Implications

- Stroke prevention clinics to improve secondary stroke prevention (effective, consistent prevention with early recognition of risk factors and timely, targeted interventions).
- Optimization of 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.

Implementation Resources and Knowledge Transfer Tools

- Canadian Cardiovascular Society
- CHEST Guidelines

Performance Measures

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

Summary of the Evidence

**LINK to Evidence Tables for Antiplatelet Therapy in Stroke and TIA Patients**

Substantial evidence from randomized trials and meta-analyses supports the use of antithrombotic agents in patients who have experienced an ischemic stroke. The most commonly recommended antiplatelet agents for secondary stroke prevention in North America and Europe are acetylsalicylic acid (ASA), clopidogrel and the combination of ASA and extended-release dipyridamole.65–67 Although some controversy regarding ASA dosage still exists, most guidelines recommend medium dose ASA (75 to 325 mg/day) as the first choice in secondary prevention of stroke. Other antiplatelet agents are acceptable alternatives. For patients with a stroke due to a cardioembolic source (e.g., atrial fibrillation, mechanical heart valve), warfarin is generally recommended (see recommendation 2.6, “Antithrombotic therapy in atrial fibrillation”) unless contraindicated. Warfarin is not recommended for secondary stroke prevention in patients presumed to have a non-cardioembolic stroke or transient ischemic attack.

**Systematic reviews**
In a critical review by O’Donnell and colleagues, immediate and long-term ASA therapy was found to reduce the risk of recurrent stroke, myocardial infarction and vascular-related death for patients with ischemic stroke or transient ischemic attack.66 Oral anticoagulation was not more effective than ASA. In comparison to ASA, long-term clopidogrel reduces the relative risk of stroke, myocardial infarction or vascular death by approximately nine percent. Any benefit of combination antiplatelet therapy with clopidogrel and ASA appears to be offset by an increased incidence of major bleeding complications compared with either agent alone. The combination of ASA and extended-release dipyridamole appeared to reduce the relative odds of stroke, myocardial infarction or vascular death by about 18 percent (OR 0.82, 95% CI 0.74–0.91) compared with ASA alone, without causing more bleeding.140

Verro and associates recently published a review of randomized controlled trials comparing ASA plus dipyridamole with ASA alone in patients with stroke and transient ischemic attack to determine the efficacy of these agents in preventing recurrent vascular events.69 Separate analyses of the incidence of stroke alone and the composite outcome of stroke, myocardial infarction or vascular death were performed, as well as two a priori subset analyses examining effect size based on trials using (1) exclusively immediate-release and (2) predominantly extended-release dipyridamole. Results indicated a significant reduction in the overall risk ratio in favour of ASA plus dipyridamole for stroke (RR 0.77, 95% CI 0.67–0.89) and for the composite end point (RR 0.85, 95% CI 0.76–0.94). Studies using immediate-release dipyridamole showed a non-statistically significant trend in favour of the combination for stroke (RR 0.83, 95% CI 0.59–1.15) and for the composite outcome (RR 0.95, 95% CI 0.75–1.19). Studies using predominantly extended-release dipyridamole showed a statistically significant difference in favour of the combination for stroke (RR 0.76, 95% CI 0.65–0.89) and for the composite outcome (RR 0.82, 95% CI 0.73–0.92). These findings indicate that ASA in combination with dipyridamole was more effective than ASA alone in preventing recurrent stroke in patients with minor stroke or transient ischemic attack.69 The risk reduction was greater and statistically significant for studies using primarily extended-release dipyridamole, which may be a reflection of a true pharmacologic effect or lack of statistical power in studies using immediate-release dipyridamole.

A 2007 review surveyed the clinical trials and guidelines concerning the use of antiplatelet therapy in the prevention of recurrent stroke after transient ischemic attack or ischemic stroke of arterial origin.100 Meta-analyses of the results from the randomized controlled trials demonstrated that, compared with control, the relative risk reduction for recurrent stroke and other serious vascular events was 13 percent with ASA, 13 percent with dipyridamole (95% CI 4% to 21%; p = 0.046) and 34 percent with combination ASA and dipyridamole. Compared with ASA, the relative risk of recurrent stroke and other serious vascular events was reduced by 7.3 percent with clopidogrel (95% CI ~5.7% to 18.7%) and 18 percent with combination ASA and dipyridamole (9% to 26%, p = 0.0003). Long-term treatment with the combination of ASA and clopidogrel was not significantly more effective in preventing serious vascular events than clopidogrel alone, mainly due to an increased frequency of bleeding complications among patients receiving both agents.

An updated Cochrane systematic review assessed the efficacy and safety of dipyridamole relative to control in the secondary prevention of vascular events in patients with vascular disease.101 The review included randomized long-term secondary prevention trials with concealed
treatment allocation, treatment for more than one month, starting within six months after presentation of an arterial vascular disease. Treatment consisted of dipyridamole with or without other antiplatelet drugs compared with no drug or an antiplatelet drug other than dipyridamole. Twenty-seven trials were included, with 20 242 patients, among whom 1399 vascular deaths and 3090 fatal and nonfatal vascular events occurred during follow-up. Compared with control, dipyridamole had no clear effect on vascular death (RR 1.02, 95% CI 0.90–1.17). This result was not influenced by the dose of dipyridamole or type of presenting vascular disease. In the presence of ASA, dipyridamole appeared to reduce the risk of vascular events compared with control (RR 0.90, 95% CI 0.82–0.97), due to a single large trial (Second European Stroke Prevention Study [ESPSP2]) in patients presenting with cerebral ischemia.144 The authors concluded that for patients who presented with arterial vascular disease, there was no evidence that dipyridamole, in the presence or absence of another antiplatelet drug, reduced the risk of vascular death, though it may reduce the risk of further vascular events. However, this benefit was found in only one large trial and only in patients presenting after cerebral ischemia. There was no evidence that dipyridamole alone was more efficacious than ASA.

The Antithrombotic Trialists’ Collaboration produced a meta-analysis of randomized controlled trials for antiplatelet therapy in high risk patients.96 The findings indicated that ASA and other forms of antiplatelet drugs reduced the incidence of nonfatal stroke by one-quarter. Absolute reduction in the rates of having a serious vascular event were 36 (standard deviation [SD] 6) per 1000 patients treated for two years among those patients with previous stroke or transient ischemic attack. The authors concluded that the benefits of ASA and other antiplatelet drugs substantially outweigh the absolute risks of major extracranial bleeding.

In a meta-analysis, Hankey and coworkers assessed the effectiveness and safety of thienopyridine derivatives (ticlopidine and clopidogrel) compared with ASA for the prevention of serious vascular events in high-risk patients.103 Four high-quality and comparable trials, including 22 656 patients at high risk for adverse vascular events, were identified (three compared ASA to ticlopidine and one compared ASA to clopidogrel). The use of a thienopyridine was associated with a marginally significant reduction in the odds of serious vascular event (12.0% v. 13%; OR 0.91, 95% CI 0.84–0.98; p = 0.01). There was also a reduction in stroke events in favour of thienopyridines compared with ASA (5.7% v. 6.4%; OR 0.88, 95% CI 0.79–0.98) corresponding to an avoidance of 7 (95% CI 1–13) stroke events per 1000 patients treated for two years. In a subgroup analysis of patients with ischemic stroke or transient ischemic attack, the results were similar to those of all patients combined; however, thienopyridine allocation was associated with a larger absolute reduction in stroke (10.4% v. 12.0%; OR 0.86, 95% CI 0.75–0.97) with an avoidance of 16 (95% CI 3–28) stroke events per 1000 patients treated for two years.103

A review by Halkes and colleagues studied five trials of dipyridamole plus ASA versus ASA alone for secondary prevention of stroke or TIA, and included the ESPRIT results.104 A total of 7612 patients A total of 7612 patients were included in the analyses (five trials). The trial-adjusted hazard ratio (HR) for composite event of vascular death, non-fatal myocardial infarction and non-fatal stroke was 0.82 (95% confidence interval, 0.72 to 0.92). Hazard ratios did not differ in subgroup analyses based on age, sex, qualifying event, hypertension, diabetes, previous stroke, ischemic heart disease, ASA dose, type of vessel disease and dipyridamole formulation, nor across baseline risk strata as assessed with two different risk scores. Dipyridamole plus ASA was more effective than ASA alone in preventing recurrent stroke; HR 0.78 (95% CI 0.68 to 0.90). The dose of ASA was fixed in four trials: 25 mg twice daily, 300 mg three times daily, 325 mg three times daily or 330 mg three times daily. In ESPRIT, the dose of ASA was left to the discretion of the treating physician, provided it was between 30 and 325 mg daily. The investigators concluded the combination of ASA and dipyridamole is more effective that ASA alone in patients with TIA or ischemic stroke of presumed arterial origin in the secondary prevention of stroke and other vascular events. The superiority was found in all subgroups and was independent of baseline risk.

**Clinical trials**

The most recent trial, SPS3, examined the effects of antiplatelet therapy on lacunar strokes that occur as a result of cerebral small vessel disease.110 This double blind randomized trial compared daily clopidogrel to placebo, with both groups also receiving 325 mg of aspirin daily. The results demonstrated that the risk of recurrent stroke was not significantly reduced with aspirin and clopidogrel (dual antiplatelet therapy) (125 strokes; rate, 2.5% per year) as compared with aspirin alone (138 strokes, 2.7% per year) (hazard ratio, 0.92; 95% confidence interval [CI], 0.72 to 1.16), nor was the risk of recurrent ischemic stroke (hazard ratio, 0.82; 95% CI, 0.63 to 1.09) or disabling or fatal stroke (hazard ratio, 1.06; 95% CI, 0.99 to 1.14). However, there was a significant difference in the number of major hemorrhagic events, where the rate was almost doubled with dual antiplatelet therapy (105 hemorrhages, 2.1% per year) as compared with aspirin alone (56, 1.1% per year) (hazard ratio, 1.97; 95% CI, 1.41 to 2.71; P<0.001).

The Prevention Regimen For Effectively avoiding Second Stroke (PRoFESS) trial, randomized, double-blind study, investigated the effects of ASA plus extended-release dipyridamole versus clopidogrel on the prevention of vascular events in patients who had a transient ischemic attack or ischemic stroke within the preceding 120 days.105 Patients participating in the trial (n = 20 332 across 35 countries) were followed for a period of four years. Stroke recurrence rates were similar in both arms of the trial (9.0 percent among patients assigned to receive ASA plus extended-release dipyridamole and 8.8 percent among patients assigned to receive clopidogrel; HR 1.01, 95% CI 0.92–1.11). Nor was there a significant difference in the composite outcome of stroke, myocardial infarction or vascular death. The trial did not meet its primary end point of noninferiority for ASA plus extended-release dipyridamole versus clopidogrel.

The European/Australian Stroke Prevention Reversible Ischemia Trial (ESPRIT) group conducted a randomized controlled trial in which patients were assigned to ASA (30–325 mg daily) with (n = 1363) or without (n = 1376) dipyridamole (200 mg twice daily) within six months of a transient ischemic attack or minor stroke of presumed arterial origin.106 The primary outcome was the composite of death from all vascular
causes, nonfatal stroke, nonfatal myocardial infarction or major bleeding complication, whichever happened first. Treatment was open, but auditing of outcome events was blinded. Primary analysis was intent to treat. Mean follow-up was 3.5 years (SD 2.0). Median ASA dose was 75 mg in both treatment groups (range 30–325); extended-release dipyridamole was used by 83 percent (n = 1131) of the patients on the combination regimen. Primary outcome events arose in 173 (13%) patients on ASA and dipyridamole and in 216 (16%) on ASA alone (HR 0.80, 95% CI 0.66–0.98; absolute risk reduction 1.0% per year, 95% CI 0.1%–1.8%). Addition of the ESPRIT data to the meta-analysis of previous trials resulted in an overall risk ratio for the composite of vascular death, stroke or myocardial infarction of 0.82 (95% CI 0.74–0.91).101

Patients on ASA and dipyridamole discontinued trial medication more often than those on ASA alone (470 v. 184), mainly because of headache. Expressed differently, ESPRIT showed that 104 patients would need to be treated with the combination regimen for 1 year to prevent 1 additional vascular death, nonfatal stroke or nonfatal myocardial infarction.

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 to 162 mg/day) or placebo plus low-dose ASA (75 to 162 mg/day) or placebo plus low-dose ASA and followed them for a median of 28 months.107 The primary efficacy end point, a composite of nonfatal stroke, nonfatal myocardial infarction or vascular death, was reached by 6.8 percent of patients assigned to receive clopidogrel plus ASA and 7.3 percent of those assigned to receive placebo plus ASA (RR 0.93, 95% CI 0.83–1.05; p = 0.22). The respective rate of the principal secondary efficacy end point, which included hospitalizations for ischemic events, was 16.7 percent and 17.9 percent (RR 0.92, 95% CI 0.86–0.99; p = 0.04). Severe bleeding in 1.7 percent of patients assigned to receive clopidogrel plus ASA and 1.3 percent of those assigned to receive placebo plus ASA (RR 1.25, 95% CI 0.97–1.61; p = 0.09).107 Among patients with multiple risk factors, the primary end point was reached by 6.6% of the clopidogrel plus ASA group and 5.5 percent of the placebo plus ASA group (RR 1.2, 95% CI 0.91–1.59; p = 0.20). Death from cardiovascular causes occurred in 3.9% of patients assigned to receive clopidogrel plus ASA and 2.2 percent of those assigned to receive placebo plus ASA (p = 0.01). In the subgroup with clinically evident atherothrombosis, a marginally significant reduction in the primary end point of 6.9 percent with clopidogrel and 7.9 percent with placebo was indicated (RR 0.88, 95% CI 0.77–0.998; p = 0.046). The investigators concluded that there was a suggestion of benefit with clopidogrel treatment in patients with symptomatic atherothrombosis and a suggestion of harm in patients with multiple risk factors; however, overall, clopidogrel plus ASA was not significantly more effective than ASA alone in reducing the rate of myocardial infarction, stroke or vascular death.

The Management of Atherothrombosis with Clopidogrel in High-risk patients with recent TIA or ischemic stroke (MATCH) trial was a randomized, double-blind, placebo-controlled comparison of ASA (75 mg/day) with placebo in 7599 high-risk patients with recent ischemic stroke or transient ischemic attack and at least 1 additional vascular risk factor who were already receiving clopidogrel 75 mg/day.108 Duration of treatment and follow-up was 18 months. The primary end point was a composite of ischemic stroke, myocardial infarction, vascular death or rehospitalization for acute ischemia (including rehospitalization for transient ischemic attack, angina pectoris or worsening of peripheral arterial disease). The primary end point was reached by 596 (15.7%) of the patients assigned to receive ASA and clopidogrel, and 636 (16.7%) of the patients assigned to receive placebo plus clopidogrel (relative risk reduction 6.4%, 95% CI –4.6% to 16.3%; absolute risk reduction 1%, 95% CI –0.6% to 2.7%). Life-threatening bleeding was higher in the group assigned to receive ASA and clopidogrel (2.6%) than in the group assigned to receive placebo plus clopidogrel (1.3%) (absolute risk increase 1.3%, 95% CI 0.6% to 1.9%). Major bleeding was also increased in the group assigned to receive ASA and clopidogrel. There was no difference in mortality between the 2 groups. The investigators concluded that adding ASA to clopidogrel in high-risk patients with recent ischemic stroke or transient ischemic attack was associated with a nonsignificant reduction in major vascular events and an increase in the risk of life-threatening or major bleeding after 18 months of follow-up.

The Clopidogrel versus ASA in Patients at Risk of Ischemic Events (CAPRIE) trial randomized 19 185 symptomatic patients (one-third had experienced a previous stroke, one-third had a previous myocardial infarction, and one-third had peripheral vascular disease) to clopidogrel (75 mg) or ASA (325 mg).151 An 8.7 percent (95% CI 0.3%–16.5%; p = 0.043) reduction in the primary end point of ischemic stroke, myocardial infarction or vascular death in favour of clopidogrel was reported. Among the patients whose qualifying event was a stroke, the number needed to treat with clopidogrel instead of ASA to prevent a recurrent ischemic event was about 180 per year.109

**Pediatrics**

ASA is frequently used in children for the secondary prevention of recurrent stroke following a transient ischemic attack or stroke event.111 In adults, it has been demonstrated that treatment with ASA can reduce the risk of recurrent stroke. Data on the efficacy and optimal dosage of ASA for paediatric stroke patients are not yet available, but it is clear that no treatment is associated with increased risk of recurrent stroke.112 ASA use has been recommended as a reasonable option for secondary prevention of arterial ischemic stroke for children not at high risk of recurrent embolism or a hypercoaguable disorder.113

Clopidogrel has been studied as an alternative to ASA in children when ASA is not tolerated or failed in children with arterial ischemic stroke.114,115 Seventeen children were included in the study and started on clopidogrel at 1 mg/kg per day up to a maximum of 75 mg/day.115 Of these, eight were on clopidogrel alone and nine in combination with ASA. Two patients developed significant intracranial hemorrhage while on the combination of clopidogrel and ASA – one has recent surgery and the other had hypertension prior to the start of therapy, as well as marked cerebral atrophy. This small initial investigation concluded that clopidogrel appears to be a reasonable option in children who cannot tolerate ASA, and the combination of clopidogrel and ASA should be used with caution.

Studies have examined the use of Clopidogrel in children with heart disease for platelet inhibition and reported it safe and efficacious at similar doses reported by Soman et al for stroke patients. In one study of Clopidogrel in 46 children with heart disease, the mean age of first
The study dosage ranged from 0.1 to 0.7 mg/kg/day clopidogrel. Almost all patients received concomitant ASA therapy. The primary outcome was thrombolytic events, and after treatment no thrombotic events developed. Hematological abnormalities occurred in one child after one year of therapy and these reversed after cessation of therapy. Similarly, Li and colleagues (2008) found that clopidogrel 0.20 mg \( \cdot \text{kg}^{-1} \cdot \text{d}^{-1} \) in children 0 to 24 months of age achieved a platelet inhibition level similar to that in adults taking 75 mg/d. These studies both concluded Clopidogrel appeared safe and efficacious in children, but stressed the need for randomized controlled research trials to establish dosing and safety in children.
### Best Practice Recommendation 2.6

**Primary prevention of stroke in patients with non-valvular atrial fibrillation:**

- Patients with atrial fibrillation or atrial flutter (paroxysmal, persistent or permanent) should be stratified using a risk score index for stroke risk (e.g., CHADS2) and for the risk of bleeding, and most patients should receive oral anticoagulant therapy [Evidence Level A].
  
  a. As part of the risk stratification, patients should be assessed for additional risk factors for stroke, including age 65-74 yr, female sex, and presence of vascular disease.

- Patients with atrial fibrillation at low risk of stroke (CHADS2 = 0) should receive ASA (81-325 mg/day) [Evidence Level A].

- Patients with atrial fibrillation at intermediate risk of stroke (CHADS2 = 1) should receive oral anticoagulation therapy. The choice of OAC should be based on patient factors including age, renal function, additional health factors, likelihood of compliance, patient preferences, and costs.

  a. Most patients should receive dabigatran, rivaroxaban or apixaban (*pending approval for use in Canada*) [Evidence Level B] or warfarin [Evidence Level A]. Refer to Anticoagulant Medication Profile table 2.6 to guide choice of therapy.

  b. Acetylsalicylic acid is a reasonable alternative for some lower risk patients, depending on their individual risk/benefit profile (age <65 and absence of vascular disease) [Evidence Level A]. Refer to CCS table with CHADS scores and treatment recommendations.

- Patients with atrial fibrillation at high risk of stroke (CHADS2 ≥ 2) should receive oral anticoagulation therapy. The choice of OAC should be based on patient factors including age, renal function, additional health factors, likelihood of compliance, and patient preferences.

  a. Most patients should receive dabigatran, rivaroxaban or apixaban (*pending approval for use in Canada*) [Evidence Level A] or warfarin [Evidence Level A]. Refer to Medication Profile table 2.6 to guide choice of therapy.

- Patients with atrial fibrillation who are already well-controlled on warfarin with a stable INR (with a documented therapeutic INR greater than 70% of the time) may continue on warfarin and may not need to switch to dabigatran, or rivaroxaban, or apixaban [Evidence Level C].

  Note, in ROCKET, warfarin patients were in therapeutic range an average of 55% of the time, IQR 43 to 71%; Rely therapeutic range was 64% of the time; and in ARISTOTLE 66% of the time.

- Patients with non-valvular atrial fibrillation who are treated with warfarin should have a target INR of 2.5 (maintained in the range of 2.0 to 3.0); for patients with atrial fibrillation and mechanical heart valves, the target INR is 3.0 (range 2.5 to 3.5) [Evidence Level A].

- The combination of ASA and clopidogrel is not routinely recommended for the treatment of atrial fibrillation and should be reserved for patients in whom treatment with warfarin or the newer oral anticoagulants is not feasible [Evidence Level A].

- There is presently no evidence to recommend dabigatran, rivaroxaban, apixaban (*pending approval for use in Canada*) outside the setting of atrial fibrillation for stroke prevention [Evidence Level C].

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

- Patients with transient ischemic attack and atrial fibrillation should begin oral anticoagulation* with dabigatran, or rivaroxaban, or apixaban (*pending approval for use in Canada*), or warfarin immediately after brain imaging has excluded intracranial hemorrhage or large infarct [Evidence Level B].

- Most patients with acute ischemic stroke and atrial fibrillation should receive oral anticoagulant therapy with dabigatran, or rivaroxaban, or apixaban (*pending approval for use in Canada*) [Evidence Level A], or warfarin [Evidence Level A].
2.6.3 Enhancing anticoagulation therapy and minimizing bleeding complications

i. Patients prescribed any oral anticoagulation* for atrial fibrillation should be educated about the diagnosis of atrial fibrillation, the risk of stroke with atrial fibrillation, the importance of medication adherence, and compliance with international normalized ratio monitoring, if required [Evidence Level B].

ii. For patients with atrial fibrillation that are taking warfarin, careful dosing and consistent international normalized ratio monitoring is recommended to minimize adverse events; warfarin efficacy is dependent on maintaining therapeutic international normalized ratio control, and declines significantly when the international normalized ratio falls below 2.0 [Evidence Level A].

iii. Concomitant antiplatelet therapy with oral anticoagulation* is not recommended in patients with atrial fibrillation unless there is a specific medical indication such as a coronary stent [Evidence Level B].

iv. With the exception of patients with mechanical heart valves, the addition of acetylsalicylic acid to warfarin in patients with atrial fibrillation has not been shown to be of benefit in stroke prevention [Evidence Level B].

v. For patients prescribed dabigatran, rivaroxaban, or apixaban, renal function should be routinely monitored, and measured at least once annually [Evidence Level C].

Clinical Considerations

- Most patients presenting with stroke and TIA will have a CHADS2 score indicating the need for anticoagulation.
- The third-party funding policies for the new oral anticoagulants (OACs) may not completely align with the Canadian Best Practice Recommendations for Stroke Care. Individual clinical factors and prescribing rationale should be clearly documented and included when physicians are advocating for coverage of these medications for their patients.
- Based on clinical trial data, warfarin failure was defined as an INR out of therapeutic range more than 30% of time (i.e., stability is defined as INR in range more than 70% of time), based on findings in RE-LY, ROCKET and ARISTOTLE.
- The decision to start anticoagulant therapy is optimally made during the acute phase of hospitalization.
- The optimal timing of oral anticoagulation following acute stroke for patients in atrial fibrillation is unclear; it is common practice to wait two to fourteen days and repeat brain imaging (CT or MRI) to rule out asymptomatic intracranial hemorrhage before starting warfarin [Evidence Level C]. Physicians will often use the size of the infarct and other clinical circumstances to help judge timing to initiate anticoagulation. For example, in patients with very small strokes on imaging, anticoagulation may be initiated immediately; in patients with large strokes, initiation of anticoagulation may be deferred for several weeks.
- The RE-LY trial of dabigatran did not enroll patients within the first 14 days after stroke, or patients with severe stroke within the previous six months.156 (7 days- Aristotle).
- For some patients with acute ischemic stroke and atrial fibrillation, the individual’s preferences, level of disability, prognosis, and overall clinical status, including the size of the infarct on neuroimaging, may contraindicate oral anticoagulant therapy [Evidence Level C].
- Patient compliance plays a significant role in the effectiveness of traditional medications (e.g., warfarin) for atrial fibrillation. Given the shorter half-lives of the new classes of antithrombotics, compliance with these therapies are also very important to monitor.
- The CHA2DS2-VASC scoring system is an emerging addition that can be considered for use particularly in patients...
with intermediate risk for stroke. The CHA\textsubscript{2}-DS\textsubscript{2}-VASc has some advantages in that it includes additional clinical data considered to be more relevant to stroke. In the CHA\textsubscript{2}-DS\textsubscript{2}-VASc, age ≥ 75 years counts as 2 points instead of one as in CHADS2, and an additional age category of 65 to 74 years with a score of 1 point has been included. The presence of vascular disease (peripheral artery disease, MI, aortic plaque) and gender (i.e., female) are also included in the expanded CHA\textsubscript{2}-DS\textsubscript{2}-VASc. These additional factors may further help to define the need for anticoagulation and better prediction of risk of first hospitalization.\textsuperscript{119}

### 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.

### System Implications

- 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 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.

### Performance Measures

1. Proportion of acute ischemic stroke patients with atrial fibrillation who are treated with anti-coagulant therapy unless contraindicated (core).
2. Proportion of eligible stroke and transient ischemic attack patients with atrial fibrillation prescribed anticoagulant therapy on discharge from acute care (core).
3. Proportion of eligible stroke and transient ischemic attack patients with atrial fibrillation prescribed anticoagulant therapy after a visit to a secondary prevention clinic (core).
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, rivaroxiban, apixiban 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, physician’s 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
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Section 2: Prevention

2.6 Anticoagulant Therapy for Atrial Fibrillation

Implementation Resources and Knowledge Transfer Tools

- Thrombosis Interest Group of Canada (available at www.tigc.org)
- Canadian Cardiovascular Society http://www.ccs.ca/guidelines/cc_library_e.aspx
- Canadian Cardiovascular Society Atrial Fibrillation Pocket Guide 2012
  - http://www.ccsguidelineprograms.ca/pocket_card/2012_Afib_PG/AIFib_PG_Flipbook/index.html,

Summary of the Evidence

**LINK to Evidence Tables for Management of Atrial Fibrillation and Stroke**

Atrial fibrillation is a common arrhythmia. The prevalence of atrial fibrillation in the general population increases with age; about 12 percent of people aged over 75 years have atrial fibrillation.\(^\text{120}\)

Atrial fibrillation is a major risk factor for stroke. The presence of atrial fibrillation increases the risk of stroke approximately five-fold; the relative risk is higher still if there is associated valvular heart disease.\(^\text{121}\) Stroke risk also varies according to the presence of other risk factors and can be estimated using a score that takes into account the presence of congestive heart failure, hypertension, age, stroke and systemic embolism.\(^\text{118}\)

Atrial fibrillation most often causes stroke via embolism of thrombus from the left atrium. Several clinical trials involving many thousands of patients with AF have examined the efficacy of various antithrombotic drug regimens. The majority of the trial evidence concerns prevention of first stroke; the evidence-base for prevention of stroke recurrence in patients with AF is much smaller. Strokes due to atrial fibrillation are generally more severe than those occurring in patients in sinus rhythm. Consequently, atrial fibrillation strokes are associated with higher case-fatality, longer hospitalization, and increased disability.\(^\text{122}\)

In spite of convincing evidence-linking AF to stroke, and the benefits of warfarin therapy in reducing this risk, AF patients are often not optimally managed. An analysis by Gladstone and colleagues using data from the Registry of the Canadian Stroke Network (RCSN) examined this issue in a cohort of 597 patients presenting to hospital with an ischemic stroke and previously known atrial fibrillation.\(^\text{123}\) They found that on admission for stroke, only 40 percent of patients were on warfarin, 30 percent on antiplatelet therapy, and 29% were not on any antithrombotics. Of those taking warfarin, three fourths had a subtherapeutic INR (<2.0) at the time of stroke admission. Overall, only 10 percent of patients with acute stroke and previously known atrial fibrillation were therapeutically anticoagulated (INR >2.0) at admission. Among the high-risk subgroup of stroke patients with a history of atrial fibrillation and a previous TIA or ischemic stroke (n=323), only 18 percent were taking warfarin with a therapeutic INR at the time of admission for their recurrent stroke; 92 percent were without therapeutic anticoagulation, and 15 percent were on no antithrombolytic therapy. These findings are particularly troublesome given that all subjects selected for inclusion in this study were considered high risk for stroke according to published criteria (low and moderate risk patients were not included), were living independently, and were considered ideal candidates for warfarin therapy (patients with known contraindications to warfarin were excluded from the study).

The management of atrial fibrillation has changed significantly since 2010 with the approval of dabigatran (RE-LY trial) and rivaroxiban (ROCKET AF), and the trials on apixaban (ARISTOTLE trial) in Canada.\(^\text{124,125,126}\) These represent a new class of anticoagulants that do not require the same close monitoring and dose titration that is involved in warfarin management. Selection of appropriate anticoagulation depends on many factors including comorbidities, age, and compliance (refer to Medication Reference Guide provided in Table 2.6.1 within these guidelines).

Dabigatran:

Dabigatran is a thrombin inhibitor with a serum half-life is 12 to 17 hours, and 80% of the given dose is excreted by the kidneys. The RE-LY (Randomized Evaluation of Long-term anticoagulant therapy) study tested two doses of dabigatran against warfarin in a non-inferiority trial with a prospective, randomized, open-label (warfarin only), blinded-end-point (PROBE) design.\(^\text{124}\) Collaborators in 44 countries enrolled 18,1130 patients (mean age 71 years, 64 percent men) who had AF and at least one of: past stroke or TIA (20 percent of participants), left ventricular ejection fraction less than 40 percent, heart failure symptoms within six months (New York Heart Association class II or higher), age 75 years or higher, or 65-74 years of age plus diabetes mellitus, hypertension, or coronary heart disease. Exclusion criteria included severe valvular heart disease (including prosthetic valves), stroke within 14 days or severe stroke within six months, conditions that increase risk for hemorrhage, creatinine clearance less than 30 mL/min, active liver disease, and pregnancy. Participants were randomly allocated to receive dabigatran, 110 mg (n=6015) or 150 mg (n=6076) twice daily, or warfarin adjusted to an INR of 2.0-3.0 (n=6022), and followed for a median of two years (follow-up was 99.9 percent complete). The primary outcome was a composite of stroke or systemic embolism. Other outcomes included major hemorrhage, stroke, and death.

Dabigatran 150 mg twice daily reduced the risk of stroke or systemic embolism more than warfarin or dabigatran 110 mg twice daily. Rates of major hemorrhage were similar for warfarin and dabigatran 150 mg twice daily; dabigatran 110 mg twice daily was associated with lower rates of major hemorrhage than warfarin. Specifically, the rates of the primary outcome were 1.69 percent per year in the warfarin group, as compared with 1.53 percent per year in the group that received 110 mg bid of dabigatran (relative risk with dabigatran, 0.91; 95% confidence interval [CI],...
The only adverse effect that was significantly more common with dabigatran than with warfarin was dyspepsia. Dyspepsia occurred in 348 patients (5.8% per year) in the warfarin group and in 707 patients (11.8% per year) and 688 patients (11.3% per year) in the 110-mg and 150-mg dabigatran groups, respectively (p<0.001 for both comparisons). Elevations in the serum aspartate aminotransferase or alanine aminotransferase of more than three times the upper limit of the normal range did not occur more frequently with dabigatran, at either dose, than with warfarin. The rate of myocardial infarction was 0.53% per year with warfarin and was higher with dabigatran: 0.72% per year in the 110-mg group (relative risk 1.35; 95% CI 0.96-1.97; p=0.07) and 0.74% per year in the 150-mg group (relative risk 1.38; 95% CI 1.00-1.91; p=0.048). An as yet unpublished trial is testing dabigatran in acute coronary syndromes. Patients taking dabigatran had more gastrointestinal (GI) bleeding, twice the likelihood of dyspepsia, and dis-continued therapy almost 50% more often in the first year of therapy (CCS 2012).

Warfarin patients in the RE-LY trial had a therapeutic INR only about 64 percent of the time. This is consistent with other clinical trials and underscores the problems with warfarin therapy. To have a stroke rate similar to that of the dabigatran 150 mg twice daily group, patients assigned to warfarin in RE-LY needed to have a therapeutic INR 80 percent of the time. This degree of control is unlikely to be achieved in clinical trials or clinical practice. Ongoing questions remain about dabigatran. These include: a) the potential safety and utility of the lower, 110 mg twice daily, dose in older patients with renal impairment; b) the safety and efficacy of dabigatran in the longer term, beyond the mean follow-up of two years, which is being evaluated in an ongoing follow-up study of RE-LY patients (NCT00808067); c) the implications, if any, of there being no antidote to dabigatran; and d) the cost of dabigatran.

Rivaroxaban:
Rivaroxaban is a direct factor Xa inhibitor that has been shown to prevent venous thromboembolism in patients undergoing hip surgery more effectively than enoxaparin (ROCKET Trial 2011). The ROCKET AF trial was a multi-center, randomized, double-blind, double-dummy, event-driven trial that was conducted at 1175 participating sites in 45 countries. Enrolment included 14,264 patients who were randomly assigned to receive fixed- dose rivaroxaban (20 mg daily or 15 mg daily in patients with a creatinine clearance of 30 to 49 ml per minute) or adjusted-dose warfarin (target international normalized ratio [INR], 2.0 to 3.0). The primary end point was the composite of stroke (ischemic or hemorrhagic) and systemic embolism. Stroke or systemic embolism occurred in 188 patients in the rivaroxaban group (1.7% per year) and in 241 patients in the warfarin group (2.2% per year) (hazard ratio, 0.79; 95% confidence interval [CI], 0.66 to 0.96; P<0.001 for noninferiority). Major and clinically relevant nonmajor bleeding occurred in 1475 patients in the rivaroxaban group and in 1449 patients in the warfarin group (14.9% and 14.5% per year, respectively; hazard ratio in the rivaroxaban group, 1.03; 95% CI, 0.96 to 1.11; P = 0.44). Rates of intracranial hemorrhage were significantly lower in the rivaroxaban group than in the warfarin group (0.5% vs. 0.7% per year; hazard ratio, 0.67; 95% CI, 0.47 to 0.93; P = 0.02). Major bleeding from a gastrointestinal site was more common in the rivaroxaban group, with 224 bleeding events (3.2%), as compared with 154 events in the warfarin group (2.2%, P<0.001). The results of the ROCKET AF trial demonstrated that rivaroxaban was noninferior to warfarin. In the primary safety analysis, there was no significant difference between rivaroxaban and warfarin with respect to rates of major or non major clinically relevant bleeding. Adverse events occurred in 81.4% of rivaroxaban subjects vs. 83.1% taking warfarin, with only epistaxis and hematuria significantly more common with rivaroxaban.

Apixaban: Apixaban is also a direct Factor Xa inhibitor with a half-life of 12 hours. The ARISTOTLE trial consisted of a double-blind, double-dummy design, where 18,201 patients were randomly assigned to treatment with apixaban or dose-adjusted warfarin. The primary objective was to determine whether apixaban was noninferior to warfarin in reducing the rate of stroke (ischemic or hemorrhagic) or systemic embolism among patients with atrial fibrillation and at least one other risk factor for stroke. The primary safety outcome was major bleeding, according to the criteria of the International Society on Thrombosis and Haemostasis (ISTH). The primary outcome of stroke or systemic embolism occurred in 212 patients in the apixaban group (1.27% per year) as compared with 265 patients in the warfarin group (1.80% per year) (hazard ratio in the apixaban group, 0.79; 95% confidence interval [CI], 0.66 to 0.95; P<0.001 for noninferiority and P=0.01 for superiority). The rate of hemorrhagic stroke was 49% lower in the apixaban group than in the warfarin group, and the rate of ischemic or uncertain type of stroke was 8% lower in the apixaban group than in the warfarin group. Fatal or disabling stroke occurred in 84 patients in the apixaban group (0.50% per year) as compared with 117 patients in the warfarin group (0.71% per year) (hazard ratio, 0.71; 95% CI, 0.54 to 0.94). Major bleeding, as defined according to ISTH criteria, occurred in 327 patients in the apixaban group (2.13% per year), as compared with 462 patients in the warfarin group (3.09% per year) (hazard ratio, 0.69; 95% CI, 0.60 to 0.80; P<0.001). Overall, ARISTOTLE trial found that in patients with atrial fibrillation, apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality.

Apixaban was also compared directly to ASA in atrial fibrillation patients in the reduction of stroke. The Apixaban Versus Acetylsalicylic Acid (ASA) to Prevent Strokes in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) trial enrolled 5599 patients to receive apixaban 5 mg twice daily or ASA at a dose of 81 to 324 mg daily. The primary efficacy outcome was the occurrence of stroke (ischemic or hemorrhagic) or systemic embolism. This trial was terminated after the first planned interim analysis of efficacy.
which showed that 104 events had occurred. The effective treatment benefit was more than 4 standard deviations in favour of apixaban. Principal outcome rates (stroke or STE) were 3.7% per year with ASA/clopidogrel vs. 1.6% per year with apixaban (RR vs. ASA/clopidogrel 0.45; 0.32-0.62; P< 0.001). The rates of major bleeding were 1.2% per year with ASA/clopidogrel vs. 1.4% with apixaban (RR 1.13; P < 0.57).

Warfarin:
Warfarin has been well established as an effective medication in reducing the risk of stroke in patients with atrial fibrillation and atrial flutter. To characterize the efficacy and safety of antithrombotic agents for stroke prevention in patients who have atrial fibrillation a meta-analysis was conducted of all randomized trials published between 1966 and March 2007, identified by using the Cochrane Stroke Group search strategy.132 The analysis included 29 trials involving 28 044 patients who had non-valvular atrial fibrillation (mean age 71 years; mean follow-up 1.5 years). Most trials studied warfarin or ASA in varying dosages and intensities, but other anticoagulants (low-molecular-weight heparin, ximelagatran, and dabigatran) and other antiplatelet agents (clopidogrel, dipyridamole, indobufen, and trifusal) were also tested. There were 3003 participants assigned to placebo or control groups in 12 trials. The average stroke rate for these untreated participants was 13 percent per year in trials that were restricted to those who had previous stroke or TIA (secondary prevention trials) and 4.1 percent per year for those in primary prevention trials.

Compared with control, adjusted-dose warfarin (6 trials, 2,900 participants 20 percent of whom had previous stroke or TIA) and antiplatelet agents (6 trials, 4,876 participants 29 percent of whom had previous stroke or TIA) reduced stroke by 64 percent (95% CI 49-74%) and 22 percent (95% CI 6-35%), respectively.132 Adjusted-dose warfarin was substantially more efficacious than antiplatelet therapy (relative risk reduction, 39 percent [95% CI 22-52%]) (12 trials, 12,983 participants 23 percent of whom had previous stroke or TIA). Adjusted dose warfarin doubled the risk of intracranial and major extracranial hemorrhage; however, absolute rates of these adverse events were only 0.2 percent per year.

The largest trial comparing adjusted-dose warfarin with antiplatelet therapy was ACTIVE-W (Atrial fibrillation Clopidogrel Plaque-stabilizing therapy) that compared with warfarin, both dabigatran and apixaban are more efficacious than warfarin for the prevention of stroke and STE, while rivaroxaban is noninferior to warfarin.117 Apixaban

Warfarin anticoagulant therapy was superior to the combination of clopidogrel plus ASA (relative risk reduction, 40 percent [95% CI 18-56%]). The ACTIVE-A trial, published after the meta-analysis by Hart et al, included 7,554 participants in whom warfarin was unsuitable, randomly allocated them to receive clopidogrel plus ASA or ASA alone, and followed them for a median of 3.6 years.102 The results showed that treating 1000 AF patients for one year with clopidogrel plus ASA prevented eight major vascular events (including two fatal and three disabling strokes) and caused seven major hemorrhages (one fatal).

Published after the meta-analysis by Hart et al was the BAFTA trial (the Birmingham Atrial Fibrillation Treatment of the Aged study) which recruited 973 patients (12.5 percent of whom had previous stroke or TIA) aged 75 years or more (mean 81.5 years) from primary care, randomly assigned them to adjusted-dose warfarin (INR 2.0 - 3.0) or ASA 75 mg once daily, and followed them for a mean of 2.7 years.103 The primary endpoint was fatal or disabling stroke (ischemic or hemorrhagic), other intracranial hemorrhage, or clinically significant systemic embolism. There were 24 primary events (21 strokes, two other intracranial hemorrhages, and one systemic embolus) among participants assigned warfarin and 48 primary events (44 strokes, one other intracranial hemorrhage, and three systemic emboli) among those assigned ASA (annual risk 1.8% vs. 3.8%, relative risk reduction 52 percent [95% CI 20-72%], p=0.003; treat 50 patients for one year to prevent one event). The annual risk of extracranial hemorrhage was 1.4 percent for patients assigned warfarin and 1.6 percent for those assigned ASA.

Two trials in the meta-analysis by Hart et al included only patients who recently had a stroke or TIA. The European Atrial Fibrillation Trial (EAFT) involved 455 patients who were within three months of TIA or minor stroke, randomly assigned them to warfarin (INR 2.5 to 4.0) or ASA (300 mg/day), and followed them for a mean of 2.3 years.106 In the Studio Italiano Fibrillazione Atrial (SIFA) trial,916 patients within 15 days of TIA or minor stroke 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.133 The combined results showed that anticoagulants were significantly more effective than antiplatelet therapy for the prevention of all ischemic vascular events (odds ratio 0.67, 95% CI 0.50–0.91) and for the prevention of stroke recurrence (odds ratio 0.49, 95% CI 0.33–0.72). Warfarin did not significantly increase the frequency of intracranial bleeding.135 Although major extracranial bleeding complications occurred more often in patients on warfarin (odds ratio 5.16, 95% CI 2.08–12.83), the absolute difference was small (2.8 percent per year versus 0.9 percent per year in EAFT and 0.9 percent per year versus zero percent in SIFA). Heparin anticoagulation confers no net benefit over antiplatelet therapy in patients with AF and recent (within 14 days) acute ischemic stroke.139

A Danish cohort study investigated the risks of bleeding on monotherapy compared to combined therapy in patients with atrial fibrillation.140 Records from nation-wide registries were used to identify patients with a first-time hospitalization for AF between 1997 and 2006. A total of 82,854 of 118,606 patients (69.9 percent) surviving AF hospitalization had at least 1 prescription filled for warfarin, ASA, or clopidogrel after discharge. During mean (SD) follow-up of 3.3 (2.6) years, 13,573 patients (11.4 percent) experienced a nonfatal or fatal bleeding. The crude incidence rate for bleeding was highest for dual clopidogrel and warfarin therapy (13.9 percent per patient-year) and triple therapy (15.7 percent per patient-year). Using warfarin monotherapy as a reference, the hazard ratio (95% confidence interval) for the combined end point was 0.93 (0.88-0.98) for ASA, 1.06 (0.87-1.29) for clopidogrel, 1.66 (1.34-2.04) for ASA-clopidogrel, 1.83 (1.72-1.96) for warfarin-ASA, 3.08 (2.32-3.91) for warfarin-clopidogrel, and 3.70 (2.89-4.76) for warfarin-ASA-clopidogrel. Triple therapy posed a bleeding risk, which was three times higher than the risk of bleeding for warfarin alone. The problems associated with warfarin therapy have stimulated the development of oral agents that produce more predictable anticoagulation and do not require frequent monitoring.

The Canadian Cardiovascular Society guidelines for the management of atrial fibrillation conclude that compared with warfarin, both dabigatran and apixaban are more efficacious than warfarin for the prevention of stroke and STE, while rivaroxaban is noninferior to warfarin.117 Apixaban
causes less major bleeding than warfarin, while in comparison with warfarin there is no more major bleeding with either dabigatran 150 mg or rivaroxaban. There is significantly less intracranial bleeding with each of the new agents than with warfarin. Clinical trials that directly compare dabigatran, rivaroxaban and apixaban have not been published, and the long term effects of these newer oral anticoagulants has not been studied due to their recent release. These trials will be required to provide specific guidance on choice of oral anticoagulant. At this time, physicians should consider patient factors, medical status and risks as well as likelihood of patient compliance in selecting a treatment regime in the presence of atrial fibrillation.

Figure 2.6: Canadian Cardiovascular Society Algorithm For Stroke Risk and Management Decisions in Patients with Atrial Fibrillation (Canadian Journal of Cardiology, 2012; 28:125-136).

** (awaiting official permission from published to reproduce this diagram)
Table 2.6: Oral Anticoagulants for the Prevention of Stroke in Atrial Fibrillation Patients

This table provides a summary of the pharmacotherapeutic properties, side effects, drug interactions and other important information on the four anticoagulant medications currently in use or under review 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, side effects, drug interactions and bleeding risk status should all be taken into consideration during decision-making, in addition to other information provided in this table and available elsewhere regarding these medications. (Notes: * Apixaban currently not available in Canada. Application has been submitted to Health Canada and is under review.)

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban*</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of Action</td>
<td>Direct thrombin inhibitor</td>
<td>Direct Xa inhibitor</td>
<td>Direct Xa inhibitor</td>
<td>Vitamin K antagonism of factors II, VII, IX, X</td>
</tr>
<tr>
<td>Indications</td>
<td>-Stroke prophylaxis in non-valvular atrial fibrillation -Prevention of VTE in TKA and THR</td>
<td>-Stroke prophylaxis in non-valvular atrial fibrillation -Prevention of VTE in TKA and THR</td>
<td>-Prevention of VTE in TKA and THR</td>
<td>-Prophylaxis and/or treatment of VTE, atrial fibrillation with embolization, and as an adjunct in the prophylaxis of systemic embolism after myocardial infarction, including stroke and reinfarction</td>
</tr>
<tr>
<td>Contraindications*</td>
<td>Active bleeding or significant risk factors for bleeding CrCl &lt;30 ml/min <em>(Cockcroft Gault Equation NOT eGFR)</em></td>
<td>Active bleeding or significant risk factors for bleeding CrCl &lt;30 ml/min <em>(Cockcroft Gault Equation NOT eGFR)</em></td>
<td>Active bleeding or significant risk factors for bleeding CrCl &lt;15 ml/min <em>(Cockcroft Gault Equation NOT eGFR)</em></td>
<td>Active bleeding or significant risk factors for bleeding Pregnancy</td>
</tr>
<tr>
<td>Side Effects</td>
<td>Gastritis-like symptoms; dyspepsia. Bleeding: 150 mg BID – similar bleeding risk to warfarin 110 mg BID – lower bleeding risk than warfarin. Lower risk of ICH than warfarin; Higher risk of GI bleed vs. warfarin with 150 mg BID dose</td>
<td>Bleeding: Similar risk to warfarin overall. Lower risk of ICH vs. warfarin. Higher risk of transfusion vs. warfarin. Higher risk of GI bleed vs. warfarin</td>
<td>Bleeding: Lower risk of bleeding vs. warfarin</td>
<td>Bleeding: Purple toe syndrome (rare)</td>
</tr>
</tbody>
</table>
### 2.6 Anticoagulant Therapy for Atrial Fibrillation

#### Landmark Trials

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban*</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RE-LY</strong></td>
<td></td>
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<tr>
<td><strong>NEJM 2009;361:1139-51</strong></td>
<td>Dabigatran</td>
<td>Rivaroxaban</td>
<td>Apixaban*</td>
<td>Warfarin</td>
</tr>
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<td></td>
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</tr>
<tr>
<td><strong>ROCKET-AF</strong></td>
<td>Dabigatran</td>
<td>Rivaroxaban</td>
<td>Apixaban*</td>
<td>Warfarin</td>
</tr>
<tr>
<td><strong>NEJM 2011;365:883-91</strong></td>
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<td></td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td><strong>ARISTOTLE</strong></td>
<td>Dabigatran</td>
<td>Rivaroxaban</td>
<td>Apixaban*</td>
<td>Warfarin</td>
</tr>
<tr>
<td><strong>NEJM 2011;365:981-92</strong></td>
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<tr>
<td><strong>Multiple RCTs and Meta-Analyses in both valvular and non-valvular Atrial Fibrillation</strong></td>
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</tr>
</tbody>
</table>

#### Inclusion Criteria

- Documented non-valvular AFib within 6 mos and at least 1 of:
  - Previous stroke/TIA
  - Heart failure
  - Age > 75
  - Age >65 + DM
  - HTN
  - CAD

#### Exclusion Criteria

- Severe heart-valve disorder
- Stroke within 14 days
- Severe stroke within 6 months
- Condition that increased risk of hemorrhage
- CrCl <30ml/min
- Active liver disease
- Pregnancy
- ASA > 100 mg/d

#### Inclusion Criteria

- Documented non-valvular AFib, with history of stroke, TIA, or systemic embolism or at least 2 of the following:
  - Heart failure
  - HTN
  - Age >75
  - DM

#### Exclusion Criteria

- Documented AFib or AFib plus at least one of:
  - Previous stroke, TIA, systemic embolism
  - Age >75
  - Heart failure
  - DM
  - HTN requiring treatment

#### Inclusion Criteria

- Severe heart valve disease
- TIA caused by reversible disorder
- Active IE
- Condition that increased risk of hemorrhage
- Uncontrolled HTN
- Stroke within 14 days or severe stroke within 3 months
- Significant liver disease
- Use of strong CYP 3A4 inhibitors
- Chronic NSAIDs
- Pregnancy
- HIV
- CrCl <30ml/min
- ASA >100mg/d

#### Exclusion Criteria

- Afib due to reversible cause
- Moderate or severe valvular disease
- Stroke in past 7 days
- CrCl <25 ml/min
- Need for ASA+Plavix or ASA >165 mg/d

### LANDMARK TRIAL BLEEDING RISKS

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban*</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall Bleeding</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>110 mg: 14.6%/yr</td>
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<tr>
<td>150 mg: 16.4%/yr</td>
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<tr>
<td>14.9 per 100 pt-yr</td>
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<tr>
<td>18.1%/yr</td>
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<td></td>
</tr>
<tr>
<td>RE-LY: 18.2%/yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ROCKET-AF: 14.5 per 100 pt-yr</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARISTOTLE: 25.8%/yr</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2.6 Anticoagulant Therapy for Atrial Fibrillation

<table>
<thead>
<tr>
<th>Major Bleeding</th>
<th>Rivaroxaban</th>
<th>Apixaban*</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>110 mg: 2.7%/yr</td>
<td>5.6 per 100 pt-yr</td>
<td>2.13%/yr</td>
<td>RE-LY: 3.4%/yr</td>
</tr>
<tr>
<td>150 mg: 3.1%/yr</td>
<td></td>
<td></td>
<td>ROCKET-AF: 5.4 per 100 pt-yr</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ARISTOTLE: 3.09%/yr</td>
</tr>
<tr>
<td>ICH</td>
<td>0.5 per 100 pt-yr</td>
<td>0.33%/yr</td>
<td>RE-LY: 0.74%/yr</td>
</tr>
<tr>
<td>110 mg: 0.23%/yr</td>
<td></td>
<td></td>
<td>ROCKET-AF: 0.7 per 100 pt-yr</td>
</tr>
<tr>
<td>150 mg: 0.30%/yr</td>
<td></td>
<td></td>
<td>ARISTOTLE: 0.8%/yr</td>
</tr>
<tr>
<td>GI Bleed</td>
<td>3.2%</td>
<td>0.76%/yr</td>
<td>RE-LY: 1%/yr</td>
</tr>
<tr>
<td>110 mg: 1.1%/yr</td>
<td></td>
<td></td>
<td>ROCKET-AF: 2.2%/yr</td>
</tr>
<tr>
<td>150 mg: 1.5%/yr</td>
<td></td>
<td></td>
<td>ARISTOTLE: 0.86%/yr</td>
</tr>
<tr>
<td>Drug Interactions</td>
<td>Prodrug – dabigatran exetilate (needs acidic environment for optimal absorption)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>* Note: This is NOT a complete list, rather examples of some of the more frequent or serious drug interactions with these OACs.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-glycoprotein (e.g. carbamazepine, rifampin, dexamethasone, trazodone, amiodarone, cyclosporine, diltiazem, verapamil, ketoconazole), other agents that effect bleeding</td>
<td>CYP3A4 and P-glycoprotein (e.g. anticonvulsants, rifampin, dexamethasone, trazodone, amiodarone, cyclosporine, diltiazem, verapamil,azole antifungals, macrolides, efavirenz), other agents that effect bleeding</td>
<td>CYP3A4 and P-glycoprotein (e.g. anticonvulsants, rifampin, dexamethasone, trazodone, amiodarone, cyclosporine, diltiazem, verapamil,azole antifungals, macrolides, efavirenz), other agents that effect bleeding</td>
<td>CYP2C9 and CYP3A4 (e.g. anticonvulsants, rifampin, amiodarone,azole antifungals, macrolides, efavirenz), vitamin K containing foods, other agents that effect bleeding</td>
</tr>
<tr>
<td>Time to Peak Effect</td>
<td>1-3 hours</td>
<td>3-4 hours</td>
<td>1-3 hours</td>
</tr>
<tr>
<td>Half-life</td>
<td>14-17 hours</td>
<td>7-11 hours</td>
<td>8-15 hours</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>6%</td>
<td>&gt;80%</td>
<td>66%</td>
</tr>
<tr>
<td>Excretion</td>
<td>80% renal</td>
<td>66% renal</td>
<td>25% renal</td>
</tr>
<tr>
<td>Effect of Food</td>
<td>Delayed absorption</td>
<td>Increases absorption of 20 mg dose but not 10 mg dose</td>
<td>No effect</td>
</tr>
<tr>
<td>Usual Dosing in Atrial Fibrillation</td>
<td>150mg BID</td>
<td>20mg OD</td>
<td>5mg BID</td>
</tr>
<tr>
<td></td>
<td>110mg BID</td>
<td>15mg OD (if CrCl 30-49)</td>
<td>2.5mg BID if ≥2 of: age≥80, wts≤60kg, SrCr≥133</td>
</tr>
<tr>
<td>Anticoagulation Monitoring</td>
<td>Dabigatran</td>
<td>Rivaroxaban</td>
<td>Apixaban*</td>
</tr>
<tr>
<td>----------------------------</td>
<td>------------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Anticoagulation Monitoring</td>
<td>Not Required</td>
<td>Not Required</td>
<td>Not Required</td>
</tr>
<tr>
<td>Additional Monitoring</td>
<td>SCr at baseline and at least annually</td>
<td>SCr at baseline and at least annually</td>
<td></td>
</tr>
<tr>
<td>Hold for Invasive Surgery</td>
<td>1-2 days (if CrCl &gt;50) 3-5 days (if CrCl &lt;50) Hold for 24 hours prior to ablation for atrial fibrillation</td>
<td>At least 24 hours</td>
<td>At least 24 hours</td>
</tr>
<tr>
<td>$ per month/coverage in Canada</td>
<td>Not yet covered for AFib in public drug plans $3.20/day</td>
<td>Not yet covered for AFib in public drug plans ~$3/day</td>
<td>Does not yet have AFib NOC</td>
</tr>
<tr>
<td>Post-Marketing Notes/Comments</td>
<td>-Safety reviews in multiple countries -Meta-analysis supports increased risk of MI seen in RE-LY trial</td>
<td>-Minimal post-marketing experience in atrial fibrillation</td>
<td>-No post-marketing experience in atrial fibrillation</td>
</tr>
</tbody>
</table>

Note:  * The FDA standard for drug dosing recommendations is the Cockroft-Gault equation
Best Practice Recommendation 2.7

Management of Extracranial Carotid Disease and Intracranial Atherosclerosis

*Minor revisions for 2012*

2.7 Symptomatic carotid stenosis

Patients with transient ischemic attack or non-disabling stroke and ipsilateral 50 to 99 percent internal carotid artery stenosis (measured by two concordant non-invasive imaging modalities such as dopplers, CTA, or MRA) should be evaluated by an individual with stroke expertise (neurosurgeon/vascular surgeon) and selected patients should be offered carotid endarterectomy as soon as possible, with the goal of operating within fourteen days of the incident event once the patient is clinically stable [Evidence Level A].

i. Carotid endarterectomy should be performed by a surgeon with a known perioperative morbidity and mortality of less than 6 percent [Evidence Level A].

ii. Carotid stenting may be considered for patients who are not operative candidates for technical, anatomic or medical reasons [Evidence Level A]. Interventionalists should have expertise in carotid procedures and an expected risk of peri-procedural morbidity and mortality rate of less than 5 percent.

iii. Carotid endarterectomy is more appropriate than carotid stenting for patients over age 70 years who are otherwise fit for surgery because stenting carries a higher short-term risk of stroke and death [Evidence Level A].

2.7.1 Asymptomatic and Remotely Symptomatic Carotid Stenosis

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 three months) [Evidence Level A].

i. Patients with asymptomatic carotid disease should be evaluated by a physician with expertise in stroke management [Evidence Level A].

ii. Patients should be less than 75 years old with a life expectancy of more than 5 years, and an acceptable risk of surgical complications [Evidence Level A].

iii. Carotid endarterectomy should be performed by a surgeon with a less than 3 percent risk of peri-operative morbidity and mortality [Evidence Level A].

iv. The benefits of carotid endarterectomy in women have shown mixed findings. Although the initial (5-year) results of the ACST showed no benefit in women, ten-year follow-up in the ACST trial suggest long-term benefit for both men and women [Evidence Level B]. Female sex in isolation is not an exclusion criterion for surgery, but should be considered as part of the overall risk benefit assessment with specific attention to co-morbid disease and general health status. [Evidence Level C].

v. Carotid stenting may be considered in patients 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].

2.7.3 Intracranial Stenosis

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

ii. In the SAMMPRIS trial the medical management arm included dual antiplatelet therapy with ASA 325 mg and Clopidogrel 75 mg for up to 90 days, as well as aggressive management of all vascular risk factors including blood pressure, lipids, diabetes mellitus, and other at-risk lifestyle patterns [Evidence Level A]. It is not clear if all these components are necessary for medical management. Management decisions should be based upon individual vascular risk profiles.

iii. In patients who have been managed with maximal medical therapy in the presence of intracranial stenosis and experience a recurrent stroke (as per SAMMPRIS), there is lack of clear evidence to guide further management decisions. Management decisions should be based upon individual vascular risk profiles [Evidence Level C].

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.

**Performance Measures**

1. **Proportion of stroke patients with moderate to severe (50 percent to 99 percent) carotid artery stenosis who undergo a carotid intervention procedure following an index stroke event.**
2. **Median time from stroke symptom onset to carotid endarterectomy surgery (core).**
3. **Proportion of stroke patients requiring carotid intervention who undergo the procedure within two weeks of the index stroke event.**
4. **Proportion of stroke patients with moderate carotid stenosis (50 percent to 69 percent) who undergo carotid intervention procedure following the incident stroke event.**
5. **Proportion of stroke patients with mild carotid stenosis (less than 50 percent) who undergo carotid intervention procedure following the incident stroke event.**
6. **Proportion of carotid endarterectomy patients who experience perioperative in-hospital stroke, acute myocardial infarction or death.**
7. **The 30-day in-hospital mortality rate after carotid endarterectomy and stroke rate by carotid occlusion severity.**
8. **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.**
9. **Proportion of patients who wait more than three months for carotid endarterectomy or whose surgery is cancelled because of long wait times.**
10. **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**


**Summary of the Evidence**

**LINK to Evidence Tables for Management of Extracranial Carotid Disease and Intracranial Atherosclerosis**

It has been well established that carotid endarterectomy is beneficial for stroke prevention in appropriate patients. There are three large trials of endarterectomy for symptomatic stenosis: the North American Symptomatic Carotid Endarterectomy Trial (NASCET), the European Carotid Surgery Trial (ECST), and the Veterans Affairs 309 Trial. According to a pooled analysis of these trials, endarterectomy is highly beneficial in symptomatic patients with severe (70–99 percent) angiographic stenosis (NNT = six to prevent one stroke over five years), moderately beneficial for symptomatic patients with moderate (50–69%) stenosis (NNT = 22 to prevent one stroke over five years) and not beneficial for mild (< 50%) stenosis. Guidelines on carotid endarterectomy from the American Heart Association and the Canadian Neurosurgical Society...
recommend surgery for symptomatic high-grade stenosis (70–99%), but have not been updated to include the most recent evidence regarding symptomatic patients with moderate stenosis or patients with asymptomatic stenosis.\textsuperscript{148,149}

The risks of carotid endarterectomy in relation to the timing of surgery was investigated in a systematic review of the literature on the complications of carotid endarterectomy.\textsuperscript{150} The operative risk of stroke and death was not increased in neurologically stable patients when surgery was performed early (< 3 to 6 weeks) rather than late (> 3 to 6 weeks). However, in unstable patients who underwent “urgent” endarterectomy for “stroke-in-evolution” or “crescendo transient ischemic attacks,” there was an increased perioperative risk (20%) that was significantly higher than the risk in stable patients.

A recent study by Gladstone, using data from the Registry of the Canadian Stroke Network (RCSN), examined factors associated with the timing of carotid endarterectomy surgery.\textsuperscript{151} A cohort of 1011 patients were found to have symptomatic carotid stenosis, and among those, 105 patients with severe (80% of cohort) or moderate (25% of cohort) stenosis underwent carotid endarterectomy within six months and were included in the analysis. The median time from index event to surgery was 30 days (interquartile range, 10 to 81). Overall, one third of patients (38 of 105) underwent surgery within two weeks, half (53 of 105) received surgery within 1 month, and one fourth (26 of 105) had surgery >3 months after the present event. In the multivariable analysis, early surgery (within two weeks) was significantly more likely to occur if the index event was a TIA rather than a completed stroke (OR, 2.6; 95% CI, 1.1 to 6.1). Age, sex, and degree of stenosis were not found to be significant predictors of early surgery. Over the study timeframe, there was an improvement in the median time to endarterectomy, decreasing from 74 days in 2003 to 21 days in 2006 (P = 0.022 for median regression analysis). The proportion of patients undergoing early carotid endarterectomy (within 2 weeks) improved significantly over time: 18.2% in 2003, 25.0% in 2004, 45.5% in 2005, and 44.8% in 2006 (P = 0.036; Cochran-Armitage trend test). Patients who did not undergo surgery were significantly older with more severe strokes and more comorbidities. The six-month mortality rate was 3.4% in the surgical group and 12.9% in the non-surgical group (p=0.0003).

Endarterectomy for symptomatic patients should be performed with a maximum combined perioperative stroke and death rate of six percent, according to the American Academy of Neurology guidelines\textsuperscript{152} and the Canadian Neurosurgical Society guidelines;\textsuperscript{149} the American Heart Association guidelines\textsuperscript{148} recommend a five percent rate for patients with transient ischemic attack and seven percent for patients with stroke. Women appear to have a higher perioperative risk and do not appear to benefit from carotid endarterectomy for symptomatic moderate (50–69%) stenosis,\textsuperscript{153} or when performed after greater than 2 weeks for symptomatic, high-grade (70–99%) stenosis.\textsuperscript{154} All of these guidelines recommend that endarterectomy for asymptomatic patients be performed with a maximum combined perioperative stroke and death rate of less than three percent.

For the Carotid Endarterectomy Trialists’ Collaboration, Rothwell and associates analyzed pooled data (5893 patients with 33 000 patient-years of follow-up) from the European Carotid Surgery Trial and North American Symptomatic Carotid Endarterectomy Trial.\textsuperscript{154} The findings indicated that the benefit from endarterectomy depends not only on the degree of carotid stenosis but also on several other clinical characteristics, including the timing of surgery after the presenting event. In patients with severe stenosis (70–99 percent), surgery was most effective when performed within two weeks of the index transient ischemic attack or stroke (NNT = three to prevent one stroke in five years), and this benefit declined quickly over time (NNT = 125 for patients who undergo surgery more than 12 weeks after the symptomatic event). This time-dependent decline in benefit was even more pronounced in patients with moderate stenosis (50–69%); endarterectomy performed within the first two weeks of the ischemic event was beneficial, but the benefit was lost (and there was net harm) when surgery was delayed more than three months. Therefore, the Carotid Endarterectomy Trialists’ Collaboration recommended that carotid endarterectomy should be done within two weeks of the patient’s last symptoms.

Carotid endarterectomy for asymptomatic carotid artery disease has been controversial. The Asymptomatic Carotid Atherosclerosis Study (ACAS) Group randomized 1682 asymptomatic patients with carotid artery stenosis of 60 percent or greater reduction in diameter to receive carotid endarterectomy, with daily ASA administration and medical risk factor management for all patients.\textsuperscript{155} After a median follow-up of 2.7 years, the absolute risk reduction for ipsilateral stroke was 3.0 percent for surgical patients compared with patients treated medically. The MRC [Medical Research Council] Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group randomized 3120 asymptomatic patients with substantial carotid narrowing equally between earlier carotid endarterectomy (half received carotid endarterectomy by one month, 88 percent by one year) and indefinite deferral of any carotid endarterectomy (only four percent per year received carotid endarterectomy) over a 10-year period.\textsuperscript{156} Patients were followed for up to five years (mean 3.4 years). The absolute risk reduction for ipsilateral stroke was 3.1 percent. Subgroup analyses found no significant heterogeneity in the perioperative hazards or (apart from the importance of cholesterol) in the long-term postoperative benefits. These benefits were separately significant for males and females, for those with about 70, 80 and 90 percent carotid artery narrowing on ultrasound and for those younger than 65 and 65–74 years of age (though not for older patients, half of whom died within five years from unrelated causes).

Asymptomatic carotid artery stenosis (unlike symptomatic carotid artery stenosis) is a relatively low-risk condition, and these studies confirm its natural history, although there is evidence that patients with higher degrees of asymptomatic stenosis are at a higher risk over time.\textsuperscript{156} Overall, the absolute risk reduction with carotid endarterectomy is small (3.0 percent), translating into a number needed to treat of about 33. Gladstone and Sahlas recommended that carotid endarterectomy should be considered only for carefully selected patients with carotid artery stenosis of at least 60 percent who are less than 75 years old, have a good life expectancy and are at low surgical risk.\textsuperscript{157} A similar recommendation has been issued by the American Academy of Neurology.\textsuperscript{152} They recommended in asymptomatic patients that “it is reasonable to consider carotid endarterectomy for patients between the ages of 40 and 75 years and with asymptomatic stenosis of 60 to 99 percent if the patient has an
expected 5-year life expectancy and if the surgical stroke or death frequency can be reliably documented to be < 3 percent (Level A).” The American Stroke Association included a recommendation that “patients with asymptomatic carotid artery stenosis be screened for other treatable causes of stroke and that intensive therapy of all identified stroke risk factors be pursued (Level of Evidence C).”

Practice gaps in carotid disease management have been identified. According to a Canadian study, the appropriate patients who are most likely to benefit from endarterecrazy are not always being referred, and many procedures are performed inappropriately on patients at low risk of stroke. In an Oxfordshire, United Kingdom, population-based study of transient ischemic attack and stroke patients referred for endarterectomy for > 50 percent stenosis, only six percent had surgery within two weeks of their ischemic event and only 43 percent within three months; 32 percent of patients had a recurrent stroke while awaiting endarterectomy. Stroke prevention clinics have been found to have an important role in promoting adherence to guidelines and ensuring appropriate patient selection and timely referral for this procedure. Delays from presenting event to initial assessment, carotid imaging and endarterectomy are new key indicators that should be monitored as part of stroke quality assurance programs.

A more recent meta-analysis in the British Medical Journal in 2010, which included the results from the International Carotid Stenting Study (ICSS), evaluated the relative short term safety and intermediate term efficacy of carotid endarterectomy versus carotid artery stenting. The analysis included randomized controlled trials which compared carotid endarterectomy with carotid artery stenting in patients with carotid artery stenosis with or without symptoms. The primary end point was a composite of mortality or stroke. Secondary end points were death, stroke, myocardial infarction, or facial neuropathy (as individual end points), and mortality or disabling stroke (as a composite end point). Eleven trials were included (4796 patients) in the analysis, with 10 that reported on short-term outcomes (n=4709) and nine on intermediate term outcomes (1-4 years). The peri-procedural risk of mortality or stroke was lower for carotid endarterectomy (odds ratio 0.67, 95% confidence interval 0.47 to 0.95; P=0.025) than for carotid stenting, mainly because of a decreased risk of stroke (0.65, 0.43 to 1.00; P=0.049), whereas the risk of death (1.14, 0.56 to 2.31; P=0.727) and the composite end point mortality or disabling stroke (0.74, 0.53 to 1.05; P=0.088) did not differ significantly. The odds of periprocedural myocardial infarction (2.69, 1.06 to 6.79; P=0.036) or cranial nerve injury (10.2, 4.0 to 26.1; P<0.001) was higher in the carotid endarterectomy group than in the carotid stenting group. In the intermediate term, the two treatments did not differ significantly for stroke or death (hazard ratio 0.90, 95% confidence interval 0.74 to 1.1; P=0.314). The authors concluded that carotid endarterectomy was found to be superior to carotid artery stenting for short-term outcomes but the difference was not significant for intermediate term outcomes; this difference was mainly driven by nondisabling stroke. Significantly fewer cranial nerve injuries and myocardial infarctions occurred with carotid artery stenting.

**Treatment: Carotid Endarterectomy and Stenting**

Two randomized trials that directly compared the safety of carotid stenting to carotid endarterectomy in symptomatic patients have been release this past year: the International Carotid Stenting Study (ICSS) and the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST). In the ICSS study, patients with recently symptomatic carotid artery stenosis were randomly assigned in a 1:1 ratio to receive carotid artery stenting or carotid endarterectomy. The primary outcome measure of the trial was the three-year rate of fatal or disabling stroke in any territory, which has not been analyzed yet. The main outcome measure for the interim safety analysis was the 120-day rate of stroke, death, or procedural myocardial infarction.

The trial enrolled 1713 patients (stenting group, n=855; endarterectomy group, n=858). Between randomization and 120 days, there were 34 (Kaplan-Meier estimate 4.0%) events of disabling stroke or death in the stenting group compared with 27 (3.2%) events in the endarterectomy group (hazard ratio [HR] 1.28, 95% CI 0.77—2.11). The incidence of stroke, death, or procedural myocardial infarction was 8.5 percent in the stenting group compared with 5.2 percent in the endarterectomy group (72 vs. 44 events; HR 1.69, 1.16—2.45, p=0.006). Risks of any stroke (65 vs. 35 events; HR 1.92, 1.27—2.89) and all-cause death (19 vs. seven events; HR 2.76, 1.16—6.56) were higher in the stenting group than in the endarterectomy group. Three procedural myocardial infarctions were recorded in the stenting group, all of which were fatal, compared with four, all non-fatal, in the endarterectomy group. There was one event of cranial nerve palsy in the stenting group compared with 45 in the endarterectomy group. There were also fewer haematomas of any severity in the stenting group than in the endarterectomy group (31 vs. 50 events; p=0.0197). The investigators concluded that at present, carotid endarterectomy should remain the treatment of choice for patients suitable for surgery. The primary outcome analysis of the efficacy of carotid artery stenting compared with endarterectomy is not yet available.

The CREST trial is the largest trial examining the relative effectiveness of carotid artery stenting (CAS) versus carotid endarterectomy (CEA) in preventing stroke, myocardial infarction, and death. The trial included 2502 patients with a median follow-up period of 2.5 years. 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.
years after randomization. The study results showed no significant difference in the estimated four-year rates of the primary end point between the stenting group and the endarterectomy group (7.2 percent and 6.8 percent, respectively; hazard ratio with stenting, 1.11; 95% confidence interval, 0.81 to 1.51; P=0.51). There was no differential treatment effect with regard to the primary end point according to symptomatic status (P = 0.84) or sex (P = 0.34). The four-year rate of stroke or death was 6.4 percent with stenting and 4.7 percent with endarterectomy (hazard ratio, 1.50; P=0.03); the rates among symptomatic patients were 8.0 percent and 6.4 percent (hazard ratio, 1.37; P=0.14), and the rates among asymptomatic patients were 4.5 percent and 2.7 percent (hazard ratio, 1.86; P = 0.07), respectively. Per-procedural rates of individual outcomes differed between the stenting group and the endarterectomy group: for death (0.7% vs. 0.3%, P=0.18), for stroke (4.1% vs. 2.3%, P = 0.01), and for myocardial infarction (1.1% vs. 2.3%, P = 0.03). After this period, the incidences of ipsilateral stroke with stenting and with endarterectomy were similarly low (2.0% and 2.4%, respectively; P=0.85). The investigators concluded that among patients with symptomatic or asymptomatic carotid stenosis, the risk of the composite primary outcome of stroke, myocardial infarction, or death did not differ significantly in the group undergoing carotid-artery stenting and the group undergoing carotid endarterectomy. During the peri-procedural period, there was a higher risk of stroke with stenting and a higher risk of myocardial infarction with endarterectomy.

The clinical trials and subgroup analysis reports for stenting versus endarterectomy have indicated that patient age greater than 70 years has a significant impact on primary outcomes. A preplanned meta-analysis was recently reported by the Carotid Stenting Trialists Collaboration that included patient-level data for 3433 patients with symptomatic carotid stenosis who were randomly assigned and analyzed in the Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial, the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) trial, and the International Carotid Stenting Study (ICSS). The data was pooled and analyzed with fixed-effect binomial regression models adjusted for source trial. The primary outcome event was any stroke or death. In the first 120 days after randomization (ITT analysis), any stroke or death occurred significantly more often in the carotid stenting group (153 [8.9%] of 1725) than in the carotid endarterectomy group (99 [5.8%] of 1708, risk ratio [RR] 1.53, [95% CI 1.20–1.95], p=0.0006; absolute risk difference 3.2 [1.4–4.9]). Of all subgroup variables assessed, only age significantly modified the treatment effect: in patients younger than 70 years (median age), the estimated 120-day risk of stroke or death was 50 (5.8%) of 869 patients in the carotid stenting group and 48 (5.7%) of 843 in the carotid endarterectomy group (RR 1.00 [0.68–1.47]); in patients 70 years or older, the estimated risk with carotid stenting was twice that with carotid endarterectomy (103 [12.0%] of 856 vs. 51 [5.9%] of 865, 2.04 [1.48–2.82], interaction p=0.0053, p=0.0014 for trend). In the PP analysis, risk estimates of stroke or death within 30 days of treatment among patients younger than 70 years were 43 (5.1%) of 851 patients in the stenting group and 37 (4.5%) of 821 in the endarterectomy group (1.11 [0.73–1.71]); in patients 70 years or older, the estimates were 87 (10.5%) of 828 patients and 36 (4.4%) of 824, respectively (2.41 [1.65–3.51]; categorical interaction p=0.0078, trend interaction p=0.0013). The conclusions stated by the Trialist Collaboration were that stenting for symptomatic carotid stenosis should be avoided in older patients (age ≥70 years), but might be as safe as endarterectomy in younger patients. A sub-group analysis on the influence of sex on outcomes in the CREST trial found no significant differences in the primary endpoints of stroke, myocardial infarct or death during the peri-procedural period (Howard 2011). End-point events occurred in 35 (4.3%) of 807 men assigned to carotid artery stenting compared with 40 (4.9%) of 623 assigned to carotid endarterectomy (HR 0.90, 95% CI 0.57–1.41) and 31 (6.8%) of 455 women assigned to carotid artery stenting compared with 16 (3.8%) of 417 assigned to carotid endarterectomy (1.84, 1.01–3.37; interaction p=0.064).

Intracranial Stenting:

The SAMMPRIS trial, released in 2011, is the first large open-label clinical trial that randomly assigned patients who had a recent transient ischemic attack or stroke attributed to stenosis of 70 to 99% of the diameter of a major intracranial artery to aggressive medical management alone or aggressive medical management plus percutaneous transluminal angioplasty with stenting (PTAS), using the Wingspan stent system. 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 underwent randomization, because the 30-day rate of stroke or death was 14.7% in the PTAS group (nonfatal stroke, 12.5%; fatal stroke, 2.2%) and 5.8% in the medical-management group (nonfatal stroke, 5.3%; non–stroke-related death, 0.4%) (P=0.002). Beyond 30 days, stroke in the same territory occurred in 13 patients in each group. Currently, the mean duration of follow-up, which is ongoing, is 11.9 months. The probability of the occurrence of a primary end-point event over time differed significantly between the two treatment groups (P=0.009), with 1-year rates of the primary end point of 20.0% in the PTAS group and 12.2% in the medical-management group.
### Introductory Notes About Stroke and Sleep Apnea:

Sleep apnea (OSA) is an emerging risk factor for stroke and a new section on sleep apnea has been added for the 2012 update of the Stroke prevention section of the Canadian Best Practice Recommendations for Stroke Care to recognize its important role. Sleep apnea is usually considered an ongoing condition that disrupts a person's sleep with persistent pauses in breathing or breathing becomes shallow. Patients will move out of deep sleep and into light sleep several times a night. These episodes wake the sleeper as he or she gasps for air. It prevents restful sleep and is associated with high blood pressure, arrhythmia, stroke and heart failure. (www.medicinenet.com/sleep_apnea; www.nhlbi.nih.gov/health/health-topics/topics/sleepapnea)

There are three types of sleep apnea, which include obstructive sleep apnea, central sleep apnea and mixed sleep apnea. Obstructive sleep apnea is seen most often with stroke patients and results from a relaxation of the muscles around the back of the tongue and soft palate, causing a complete or partial block to the airway and resulting in decreased oxygen levels. Central sleep apnea occurs when there are interruptions to the signals from the brain to the muscles that control breathing. Mixed sleep apnea is diagnosed when both central and obstructive sleep apnea are present.

The recommendations included in this section focus on obstructive sleep apnea (more common in patients following a stroke) assessment and management in patients who have experienced a stroke or transient ischemic attack. Healthcare providers should also be aware that stroke patients may also experience central or mixed sleep apnea, but this is much less common. In addition, many of the screening, assessment and management strategies listed below also apply to patients with diagnosed sleep apnea who are also at increased risk of a first stroke or transient ischemic attack.

### Best Practice Recommendation 2.8

**Assessment and Management of Obstructive Sleep Apnea**

* NEW Topic for 2012

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<td><strong>2.8</strong> Obstructive sleep apnea (OSA) is an emerging risk factor for stroke and has also been shown to be present in many patients following a stroke [Evidence Level B]. Preventative strategies should be in place for people with obstructive sleep apnea and stroke patients with sleep disturbance symptoms that emerge following stroke [Evidence Level B].</td>
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#### 2.8.1 Screening and Assessment for Sleep Apnea

Patients who have experienced a stroke or TIA are more likely to experience obstructive sleep apnea following their stroke compared to people who have not had a stroke [Evidence level A]. Patients who have experienced a stroke or TIA should be screened* at all transition points and follow-up visits for the presence of sleep apnea symptoms [Evidence level A], using a validated sleep apnea screening tool. (* Screening is defined as using a standardized brief clinical questionnaire to determine sleep patterns, symptoms of OSA, and likelihood that a patient may have sleep apnea – refer to Implementation Tools section for suggested tools).

i. Patients with sleep apnea post-stroke often do not display typical clinical characteristics of sleep apnea (Evidence level B); therefore initial screening for sleep apnea using a validated screening questionnaire should be considered for patients with:

   a. recurrent stroke [Evidence level A].
   b. fragmented sleep, difficulty sleeping, daytime sleepiness [Evidence level B].
   c. increased frequency of nocturia or snoring [Evidence level B].

ii. Patients with symptoms suggestive of sleep apnea on initial screening (as described in 2.8.1.i) should be referred to a sleep specialist for more detailed assessment and diagnosis [Evidence level C], which may include a more detailed sleep history, physical assessment, and a formalized sleep study [Evidence level A].

iii. Sleep apnea screening should be considered in patients with drug resistant hypertension [Evidence Level B] and atrial fibrillation [Evidence Level C].
2.8.2 Management of Obstructive Sleep Apnea in Patients with Stroke

Stroke prevention strategies, including specific targeted management strategies for sleep apnea, should be initiated for patients with confirmed sleep apnea pre or post stroke or TIA, based on objective clinical assessment and investigations [Evidence Level B].

i. The management of all treatable vascular disease risk factors should be optimized in patients with confirmed sleep apnea pre or post stroke [Evidence Level B] as described in other sections of these best practice recommendations including: blood pressure, diet, sodium intake, physical activity, obesity, alcohol reduction, smoking cessation and antithrombotic therapy.

ii. First line therapies for the treatment of sleep apnea before or following a stroke may include:
   a. Avoidance of hypnotic and sedative medications and alcohol (sedatives) [Evidence level B];
   b. Positional therapy [Evidence level B]: Patients should be advised to stay off their back where possible to alleviate apnea-type symptoms when they have received a diagnosis of supine related sleep apnea [Evidence level B].
   c. Weight loss [Evidence level B]
   d. Continuous positive airway pressure (C-PAP) [Evidence level B].
   e. Dental appliances [Evidence level B] in consultation with dental specialists.

iv. Severity of sleep apnea, presenting symptoms and patient compliance are factors that should be considered in the selection of treatment modalities [Evidence level B].

v. Determination of severity of sleep apnea should be based on clinical symptoms, sleep architecture (patterns), number of respiratory events per hour and oxygen saturation [Evidence level B].

vi. Patients and family members should be provided ongoing education, counseling and support regarding the signs, symptoms and risks of sleep apnea [Evidence Level B]; compliance with treatment to reduce stroke recurrence, and increase recovery; and, signs and symptoms of stroke and appropriate actions to take when any stroke symptoms appear [Evidence Level B].

vii. Refer to available comprehensive Sleep Apnea Guidelines for additional information on the management of sleep apnea (Refer to Canadian Thoracic Society Guidelines; American Academy of Sleep Medicine). 168,167

2.8.3 There is insufficient evidence to provide specific recommendations with respect to treatment of completely asymptomatic sleep apnea and the risks of stroke and TIA [Evidence Level C].

i. Based on expert opinion, the Canadian stroke sleep apnea writing group recommends that treatment be considered in asymptomatic patients with an AHI > 20 per hour or SaO2 < 90% for greater than 12% of total recording time [Evidence Level C]. 168

ii. The overall vascular health status of the patient (e.g., presence of hypertension, coronary artery disease, etc) should also be considered as a factor in treatment decisions [Evidence Level C].

2.8.4 Paediatric Considerations: There is no direct evidence available to demonstrate a connection in children regarding sleep apnea and stroke. However, it is recommended that children with stroke be screened for signs and symptoms suggesting sleep apnea [Evidence Level C], or conditions predisposing them to sleep apnea, such as obesity, sickle cell disease, severe strokes, or structural airway problems (e.g., enlarged tonsils) [Evidence Level C].169,170

i. Any child with suspected sleep apnea should be referred to a paediatric sleep specialist or respirologist for further assessment and decision-making regarding appropriate management [Evidence Level C].

Rationale

Sleep apnea is an emerging area of concern in stroke management. Sleep Disorders are an under recognized problem that predispose people to stroke occurrence and recurrence. Sleep apnea is a modifiable risk factor that can be treated quickly to alleviate the associated risk of stroke. Although there is a lack of randomized controlled trials, several observational studies have demonstrated that people with obstructive sleep apnea are 1.6 to 2.7 times more likely to experience a stroke. Treating patients with obstructive sleep apnea and stroke with continuous positive airway pressure has been shown to have positive effects on outcomes in the post-stroke setting. Patients with untreated sleep apnea have demonstrated poorer outcomes and increased mortality rates.
### System Implications

- Implementation of protocols for assessment of sleep disturbances or risk factors for sleep apnea in stroke patients
- Implementation of criteria to prioritize appropriate access to sleep specialists and sleep study labs as required, especially in under-resourced regions
- Regional service capacity and clearly communicated access criteria for specialized sleep medicine services
- Resources and opportunities for education on sleep apnea and correct use of screening and assessment tools for healthcare professionals
- Development of patient and family education resources on the awareness of sleep apnea as a risk factor pre and post stroke, and the importance of screening and treatment adherence

### Performance Measures

1. Proportion of patients presenting to hospital with stroke or TIA who have a history of confirmed sleep apnea.
2. Proportion of patients with stroke or TIA who are screened for sleep apnea symptoms before discharge from acute care, during inpatient or outpatient stroke rehabilitation, and/or during stroke prevention follow-up visits.
3. Proportion of patients who are screened and referred for sleep studies following a stroke or TIA.
4. Proportion of patients referred for sleep studies following a stroke or TIA who receive a confirmed diagnosis of sleep apnea.
5. Proportion of stroke and TIA patients with confirmed sleep apnea with recurrent stroke or TIA at one year and 5 years following index stroke or TIA.
6. Quality of life for patients with sleep apnea and their family members (measured at intervals to monitor changes over time with treatment).
7. Sustained weight loss for overweight or obese patients with stroke and sleep apnea at regular intervals (1 year, 2 years etc.) following achievement of target weight loss.

### Measurement Notes

- Data for these indicators will be in health professional notes and assessment sections of individual charts, and should be added to electronic health records.

### Implementation Resources and Knowledge Transfer Tools

- **Tools to screen for OSA**
  - Berlin Sleep Scale http://www.cpap-supply.com/Articles.asp?ID=178
  - Adjusted Neck Circumference (ANC)
  - Sleep Apnea Clinical Score http://www.thoracic.org/assemblies/srn/questionaires/sdq.php
- **Tools to assess daytime sleepiness**
  - Epworth Sleepiness Scale http://www.stanford.edu/~dement/epworth.html
- **Tools to assess sleep quality**
  - Pittsburg Sleep Quality Index (PSQI)

### Summary of the Evidence

**LINK to Evidence Tables For Sleep Apnea and Stroke**

Epidemiological studies have shown that the prevalence of obstructive sleep apnea ranges between 17-76%, depending on the characteristics of the cohorts included in individual studies, and the definitions of sleep apnea applied. OSA is often defined by the number of apneas/hypopneas a subject experiences per hour of sleep, or the apnea/hypopnea index (AHI), with mild OSA often being defined as >5 AHI and severe OSA often defined as ≥30 AHI.
Several large observational studies with patients with mild-severe sleep apnea have been reported, and about half include comparison groups between participants with treated and untreated sleep apnea. Study population sizes have ranged from a low of 166 participants to over 5,000 participants and included both males and females. These studies have consistently reported an increased risk of stroke and new vascular events in patients with OSA. Artz and colleagues (2005; n=1475) reported an odds ratio (OR) of 3.87 for first stroke in moderate-severe OSA patients (AHI>20) compared to patients with an AHI<5 when controlling for hypertension.\(^{166}\) Similarly, Redline and colleagues (2010; n=5422) found that the unadjusted OR for sleep apnea and stroke was 2.26 in males and 1.65 in females.\(^{171}\) For men in the highest AHI quartile (AHI>19), the adjusted hazard ratio for stroke and apnea and stroke was 2.86 (95% CI, 1.1–7.4). For men, each one-unit increase in AHI was associated with a 6% increased risk of stroke. Valham and colleagues (2008; n=392) found patients with sleep apnea (AHI>15) had an increased risk of stroke compared with patients without sleep apnea (HR of 2.89, 95% CI 1.37 to 6.09, \(P<0.005\)), and this was independent of age, body mass index, gender, left ventricular function, coronary artery intervention, diabetes mellitus, hypertension, previous stroke/transient ischemic attack, atrial fibrillation, and smoking.\(^{172}\)

Sleep disturbances may be further aggravated by stroke or even caused by stroke. Studies have found that patients with sleep apnea are often older, more obese, have suffered a previous stroke and have a higher prevalence of hypertension compared to patients without sleep apnea.\(^{173–177}\) Differences between controls and patients with stroke or TIA have been found in habitual snoring (58% v.12%), AHI (27 v.6) and in minimal oxygen saturation during sleep (82% v. 89).\(^{178}\) Stroke type (ischemic versus hemorrhagic stroke) has been found to be significantly associated with having an AHI>20 (OR 4.5 [1.2–16.8]) and stroke severity has been associated with poststroke sleep apnea.\(^{179}\)

Unrecognized and untreated sleep disorders may adversely influence rehabilitation efforts and outcomes, and increase the rate of stroke recurrence. Ianzro and colleagues (2002) found that early neurologic worsening in first-ever hemispheric ischemic stroke patients was associated with sleep apnea (OR of 8.2; 95% CI, 1.3-51.2; \(p=0.018\)) and higher AHI (\(p=0.011\)).\(^{180}\) Kaneko and colleagues (2003) found stroke patients with sleep apnea had worse functional capacity, as measured by the FIM, both at admission and at discharge from a rehabilitation unit, and that for every 10-unit increase in AHI, the functional independence measure (FIM) score decreased by 2.3.\(^{181}\) Stroke patients with sleep apnea also spent 30% more time in the hospital compared to patients without sleep apnea (\(p<0.05\)). It has also been found that the rate of stroke recurrence is significantly and independently higher in patients with obstructive sleep apnea (OR=1.52, \(P<0.05\)).\(^{182}\)

Sleep apnea has also been associated with drug-resistant hypertension. Demede and colleagues (2011) found that patients with resistant-hypertension were at higher risk of having sleep apnea compared to non-resistant hypertension patients (\(OR = 2.46, 95\% CI: 1.03–5.88, P < .05\)).\(^{183}\) Similarly, Friedman and colleagues (2010) found that AHI severity was greater in patients with drug-resistant hypertensive than in a controlled hypertension group (AHI: 43.0 \(\pm\) 18.3 versus 14.6 \(\pm\) 6.5). For men in the highest AHI quartile (AHI>20) compared to patients with an AHI<5 when controlling for hypertension, the adjusted odds ratio for the association between atrial fibrillation and sleep apnea was 3.04 (95% CI 1.24–7.46; \(P=0.02\)).\(^{184}\) Untreated sleep apnea was also associated with recurrence of atrial fibrillation after cardioversion procedures (\(p=0.013\)).\(^{185}\) In a recent meta-analysis of almost 4,000 patients, 4 studies demonstrated that the presence of obstructive sleep apnea increased the risk of atrial fibrillation recurrence after catheter ablation, and 2 showed no significant difference using multivariate analysis.\(^{186}\) The authors found that OSA patients had a 25% greater risk of atrial fibrillation recurrence after catheter ablation compared to controls (RR 1.25, 95% CI 1.08 to 1.45, \(P=0.003\)); however, the heterogeneity test showed significant differences among the individual studies (chi-square \(=9.77, p = 0.08, I^2 = 49\%\)).

With evidence suggesting sleep apnea is an independent risk factor for stroke and that sleep-disordered breathing may be exacerbated by stroke, the next question to address is whether treatment of sleep apnea reduces the risk of stroke and other serious vascular events. There are several treatment modalities that might be considered including positional therapy, surgery, lifestyle modification, dental appliances, and continuous positive airway pressure (CPAP). Svatikova and colleagues (2011) found that the use of positional therapy to treat sleep apnea in an ischemic stroke population reduced the absolute percentage of time spent in a supine position while sleeping by 36% (95% CI: 18–55%, \(P < 0.001\)) and reduced AHI by a relative 19.5% (95% CI: 4.9–31.9%, \(P = 0.011\)).\(^{192}\)

A Cochrane review investigated the use of surgery to treat obstructive sleep apnea.\(^{193}\) A meta-analysis was not possible and the authors found that the studies identified in the review did not provide evidence to support the use of surgery in sleep apnea/hypopnoea syndrome, as overall significant benefit was not demonstrated. Long-term follow-up of patients who undergo surgical correction of upper airway obstruction is required to aid in identifying suitable treatment and candidates for surgery.
Continuous positive airway pressure therapy has been shown to significantly reduce the occurrences of Paroxysmal Atrial Fibrillation (P < 0.001); improve sleep-related symptoms; and may prevent the occurrence of new vascular events. Giles and colleagues (2006) found CPAP improved Epworth Sleepiness Scale scores compared to controls, reduced AHI compared to oral appliances, improved sleep efficiency, and improved minimum oxygen saturation. Martínez-Garcia and colleagues (2011) found that patients with moderate-severe obstructive sleep apnea (AHI ≥ 20) who could not tolerate CPAP showed an increased adjusted incidence of new ischemic strokes (HR 2.87, 95% CI 1.11-7.71, p = 0.03), compared to patients with moderate-severe OSA who tolerated CPAP.

It has also been reported that CPAP use is associated with improved poststroke outcomes. In a randomized trial, Bravata and colleagues (2011) found that stroke patients randomized to CPAP treatment had greater median improvement in NIHSS (-3.0) than control patients (-1.0), p = 0.03. The greatest improvement was observed in patients who started CPAP therapy within 48 hours of stroke onset. Hsu and colleagues (2006) found that CPAP use was positively correlated with a better Barthel Index scores (p = 0.035) and language scores (ACE subscale) (p = 0.013) amongst stroke patients with sleep apnea. Similarly, Parra and colleagues (2011) found that the percentage of patients with neurological improvement 1 month after stroke was significantly higher in the CPAP group (Rankin scale 90.9 vs. 56.3% (p<0.01); Canadian scale 88.2 vs. 72.7% (p<0.05)). In a randomized trial, CPAP use was associated with improved blood pressure in patients with drug-resistant hypertension. Patients who used CPAP for more than 5.8 hours a night showed a greater reduction in daytime diastolic BP (-6.12mmHg, CI -1.45; -10.82, P = 0.004), 24-h diastolic BP (-6.98mmHg, CI -1.86; -12.1, P = 0.009) and 24-h systolic BP (-9.71mmHg, CI -0.20; -19.22, P = 0.046). Studies consistently report, however, that CPAP adherence rates are low among sleep apnea patients.

Brown and colleagues (2005) explored the cost-effectiveness of screening for sleep apnea in patients with acute ischemic stroke. A decision tree modeled 2 alternative strategies: polysomnography followed by 3 months of CPAP for those found to have OSA versus no screening. The primary outcome was the utility gained through screening and treatment in relation to two willingness-to-pay thresholds of $50 000 and $100 000 per quality-adjusted life year (QALY). Screening resulted in an incremental cost-effectiveness ratio of $49 421 per QALY. Screening was a cost-effective option as long as CPAP treatment improves patient utilities by >0.2 for a willingness-to-pay of $50 000 per QALY. These results are preliminary and clinical trials are required to further investigate the effectiveness of CPAP and oral appliances in improving stroke outcomes in patients with obstructive sleep apnea.
Smoking cessation has been found to reverse/reduce stroke risk as duration of being smoke known to be an important and effective provider tool to close the gap between recommended care and actual care provided. Moreover, even brief interventions by providers are known to be effective in increasing the likelihood of a quit attempt by a person who smokes. People who are not ready to quit should be offered a motivational intervention to help enhance their readiness to quit.

Canadians are current smokers, and a large proportion has been shown to be willing to make a quit attempt. The three classes of pharmacological agents that should be considered as first-line therapy for smoking cessation are nicotine replacement therapy, bupropion, and varenicline. The choice of appropriate pharmacotherapy should take into account the patient’s medical stability, clinical needs, other medical factors, and patient preferences. People who are not ready to quit should be offered a motivational intervention to help enhance their readiness to quit. Smoking cessation should be identified, assessed and documented.

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

Rationale
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 significance 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

- A focus on arterial health for paediatric cases—such as diet, exercise, non-smoking, avoidance of drugs that increase stroke risk.
- Access to risk factor management programs such as smoking cessation programs should be available in all communities, primary healthcare settings and workplaces.
- Government actions to restrict smoking in public areas and discourage smoking through legislation and taxation initiatives.
- Coordinated efforts among stakeholders such as Heart and Stroke Foundations (national and provincial), the Canadian Stroke Network, 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 process 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 advertising the availability of educational material, effective dissemination mechanisms and follow-up.
- Educational resources, that are culturally and ethnically appropriate, are available in multiple languages and that address the needs of patients with aphasia.

### Performance Measures

1. Proportion of patients with documented smoking status recorded on patient record.
2. Proportion of patients with stroke and TIA with a history of cigarette smoking who are given smoking cessation advice and counseling during acute hospital stay, inpatient and outpatient rehabilitation, and during secondary prevention visits.
3. 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.

### Implementation Resources and Knowledge Transfer Tools

- **Canadian Best Practice Recommendations for Stroke Care Smoking Cessation Pharmacology Summary Table** (weblink)
- **CAN-ADAPTT Smoking Cessation Guidelines**
  https://www.nicotinedependenceclinic.com/English/CANADAPTT/Pages/Home.aspx
- **CAN-ADAPTT Tool Kit**
  http://knowledgex.camh.net/primary_care/toolkits/addiction_toolkit/smoking/Pages/tools_resources.aspx
- **Smoking Cessation and the Cardiovascular Specialist: Canadian Cardiovascular Society Position Paper.**
  http://www.onlinejc.ca/article/S0828-282X(10)00076-0/fulltext
- **QUIT NOW - Health Canada Smoking Cessation**
- **CADTH Smoking Cessation Pharmacology 2011.**
  http://www.cadth.ca/media/pdf/CADTH_Smoking_Cessation_Summary_for_Health_Care_Providers_e.pdf
- **Canadian Public Health Association:**
- **US Tobacco guidelines**
- **Skills and tools for clinicians on motivational interviewing (handouts, self-evaluations, checklists):**
  [http://www.motivationalinterview.org/clinicians/Side_bar/skills_maintenence.html](http://www.motivationalinterview.org/clinicians/Side_bar/skills_maintenence.html)
- **The Motivational Interviewing Assessment: Supervisory Tools for Enhancing Proficiency (manual):**
- **The Change Book:**
- **The Change Book Workbook:**
- **Contemplation latter:**
- **Readiness-ruler -**
## Summary of the Evidence

**LINK to Evidence Tables for Management of Smoking Cessation**

Tobacco smoking remains a significant risk factor for many chronic diseases including cardiovascular disease. In Canada, the Public Health Agency of Canada report on cardiovascular disease found that 15.3 percent of the population over the age of twelve self-reports being active smokers in 2007; this is an improvement from 19.9 percent reported in 2000. Smoking policies and regulations have made notable progress over that same timeframe. The United States Department of Health and Human Services has stated that tobacco “presents a rare confluence of circumstances: (1) a highly significant health threat; (2) a disinclination among clinicians to intervene consistently; and (3) the presence of effective interventions.” The World Health Organization “M-Power” report describes smoking as a global tobacco epidemic. In that report, 6 policies were recommended to reverse the tobacco epidemic, all of which are targeted at the national level. These policies are tobacco use and prevention policies; protection of people from tobacco smoke; assistance in quitting tobacco use; warnings about the dangers of tobacco; enforcement of bans on tobacco advertising, promotion and sponsorship; and raising taxes on tobacco.

Research has demonstrated that current smokers who smoke 20 or more cigarettes per day have an associated increase of stroke risk approximately 2 to 4 times that of non-smokers. Overall, given that an estimated 25 percent of adults are active smokers, approximately 18 percent of strokes may be attributed to active smoking.

Smoking acts as a risk factor in a dose-dependent fashion, such that heavy smokers have more risk than light smokers, who in turn have more risk than nonsmokers. Results of a recent study demonstrated that the relative risk for ischemic stroke associated with smoking fewer than 20 cigarettes per day was 1.56 when compared with non-smokers and 2.25 when 20 or more cigarettes were smoked per day. Reported relative risks for hemorrhagic stroke among smokers followed a similar pattern. Within a male population, smoking fewer than 20 cigarettes was associated with a 1.6-fold increase for intracerebral hemorrhage and a 1.8-fold increase for subarachnoid hemorrhage compared with non-smokers. When the rate of smoking increased to 20 cigarettes or more, the associated risk increased to 2.1 and 3.2 for intracerebral hemorrhage and subarachnoid hemorrhage, respectively. A study conducted within a female subject population yielded a similar pattern of risk.

Risk associated with current cigarette smoking is greatest in the middle years and declines with age. The Cardiovascular STudy in the ELderly (CASTEL) reported that the relative risk associated with current smoking compared with current non-smokers was 1.60 for fatal stroke. Mortality was particularly high among current smokers who had been smoking for 40 or more years (7.2% v. 1.8% for non-smokers, p < 0.01).

There is a growing body of evidence examining smoking cessation interventions in adolescents and parental groups to protect young children from second-hand smoke. Next to alcohol, the most commonly used substance among college students is tobacco. Audrian-McGovern and colleagues (2011) found in adolescents, those who received motivational interview-based interventions were about 60% less likely to try to quit smoking than those who received structured brief advice (OR: 0.41 [CI: 0.17– 0.97]). However, adolescents who received motivational interviewing showed a greater reduction in cigarettes smoked per day than adolescents who received structured brief advice (5.3 vs. 3.3 fewer cigarettes per day). Parental quit-strategies that took place in hospitals, pediatric clinical settings, well-baby clinics, and family homes were found to successfully increase parental quit rates. Children aged 4-17 were found to benefit significantly from parental smoking cessation.

There are several non-pharmacotherapy interventions that have been shown to be effective smoking cessation interventions. In a recent Cochrane Review, it was found that smoking cessation interventions that used behavioural therapy strategies, either solely or in combination with pharmacotherapy, produced a significant effect in favour of the intervention (RR=1.43, 95% CI 1.03-1.98, p=0.032). Similarly, Cabzeas and colleagues (2011) examined the effects of a behavioural based smoking cessation
The intervention included brief motivational interviews for smokers at the precontemplation–contemplation stage, brief intervention for smokers in preparation–action who do not want help, intensive intervention with pharmacotherapy for smokers in preparation–action who want help and reinforcing intervention in the maintenance stage. Control group involved usual care. The 1-year continuous abstinence rate at follow-up was 8.1% in the intervention group and 5.8% in the control group (P = 0.014). The odds of quitting of the intervention versus control group was 1.50 (95% confidence interval = 1.05–2.14).

Ussher and colleagues (2012) performed a Cochrane Review to determine whether exercise-based interventions were an effective smoking cessation tool. They found three studies that showed significantly higher abstinence rates in a physically active group versus a control group at end of treatment.

A systematic review and meta-analysis of smoking cessation therapies found that Bupropion trials were superior to controls at one year (12 RCTs, OR 1.56, 95% CI, 1.10–2.21, P = 0.01) and at three months (OR 2.13, 95% CI, 1.72–2.64). Two RCTs evaluated the superiority of bupropion versus NRT at one year (OR 1.14, 95% CI, 0.20–6.42, P =< 0.0001) and also at approximately 3 months (OR 3.75, 95% CI, 2.65–5.30). Three RCTs evaluated the effectiveness of varenicline versus bupropion at 1 year (OR 1.58, 95% CI, 1.22–2.05) and at approximately three months (OR 1.61, 95% CI, 1.16–2.21). Using indirect comparisons, varenicline was superior to NRT when compared to placebo controls (OR 1.66, 95% CI 1.17–2.36, P = 0.004) or to all controls at one year (OR 1.73, 95% CI 1.22–2.45, P = 0.001). This was also the case for three-month data. Adverse events were not systematically different across studies. A study that examined the effects of bupropion for relapse prevention found that it was associated with a higher point-prevalence for smoking abstinence compared to placebo (p=.007), and this was independent of past history of depression.
### Table 2.9: 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.

<table>
<thead>
<tr>
<th></th>
<th>Nicotine patch</th>
<th>Nicotine gum</th>
<th>Nicotine inhaler</th>
<th>Nicotine Lozenge</th>
<th>Bupropion</th>
<th>Varenicline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial Treatment Length</strong></td>
<td>8-12 weeks</td>
<td>4-36 weeks</td>
<td>12-24 weeks</td>
<td>4-24 weeks</td>
<td>7-12 weeks</td>
<td>12-24 weeks</td>
</tr>
<tr>
<td><strong>Time to Peak Effect</strong></td>
<td>Requires 2-3 days to get maximal serum levels</td>
<td>After 20-30 min of chewing</td>
<td>Within 15 minutes after forced inhalation for 20 minutes</td>
<td>After 20-30 min of sucking</td>
<td>1-2 weeks</td>
<td>1-2 weeks</td>
</tr>
<tr>
<td><strong>Indications</strong></td>
<td>As an aid to smoking cessation</td>
<td>As an aid to smoking cessation, major depressive disorder, seasonal affective disorder</td>
<td>As an aid to smoking cessation</td>
<td>As an aid to smoking cessation</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Usual Dosing</strong></td>
<td>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 then 10mg for 2 weeks then 5mg for 2 weeks</td>
<td>&lt;25 cig/d or smokers &gt;30 min upon waking: 2 mg &gt;25 cig/d or smokers &lt;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</td>
<td>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</td>
<td>Polacrilex: Smokes &gt;30 min upon waking: 2mg Smokes &lt;30 min upon waking: 4mg Bitartarate: &lt;20 cig/d: 1 mg &gt;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</td>
<td>150 mg once daily x 3 days then 150 mg BID x 7-12 weeks. Begin 1-2 weeks prior to selected quit date</td>
<td>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</td>
</tr>
<tr>
<td>Special Dosing Notes</td>
<td>Nicotine patch</td>
<td>Nicotine gum</td>
<td>Nicotine inhaler</td>
<td>Nicotine Lozenge</td>
<td>Bupropion</td>
<td>Varenicline</td>
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<tr>
<td>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 21 mg patches plus gum or inhaler for cravings. In the “Reduce to Quit” approach, patients may continue to smoke while on the patch as they are receiving nicotine via the patch/gum/lozenge/inhaler and should be smoking fewer cigarettes, which is the goal.</td>
<td>Must titrate dose when discontinuing</td>
<td>Upward titration to reduce nausea from drug</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side Effects</td>
<td>Headache, GI upset, dizziness, nausea, disturbed sleep, rash at site</td>
<td>Headache, GI upset, hiccups, disturbed sleep, sore jaw</td>
<td>Irritation of throat and nasal passages, sneezing, coughing especially in those with bronchospastic disease, hiccups</td>
<td>GI upset, mouth/throat soreness, hiccups</td>
<td>Dry mouth, insomnia, agitation, vivid dreams, unease. Risk of seizure is 1/1000 (risk factors include those with seizure or eating disorders)</td>
<td>Nausea, insomnia, abnormal/vivid dreams, Health Canada warning for psychiatric effects</td>
</tr>
<tr>
<td>Effect of Food and Other Administration Notes</td>
<td>Do not cut patch, causes rapid evaporation rendering product useless. Rotate patch site to avoid skin irritation.</td>
<td>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.</td>
<td>Not a true inhaler (is a vaporizer) so best effect with continuous puffing; nicotine absorbed from oral mucosa. Cold temperatures can decrease absorption rate.</td>
<td>Recent food and beverage impairs release of nicotine. Avoid food and drink 15 min before or while using lozenge.</td>
<td>Sustained release product; do not crush or chew.</td>
<td></td>
</tr>
<tr>
<td>Drug Interactions</td>
<td>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).</td>
<td></td>
<td></td>
<td></td>
<td>Inhibits CYP2D6, 2B6 substrate, avoid with MAOI</td>
<td>Increased adverse effects if combined with NRT</td>
</tr>
<tr>
<td>Contraindications/Cautions</td>
<td>Life-threatening arrhythmias, severe angina, atopic/eczematous dermatitis or other skin conditions (e.g. psoriasis)</td>
<td>Life-threatening arrhythmias, severe angina</td>
<td>Life-threatening arrhythmias, severe angina</td>
<td>Life-threatening arrhythmias, severe angina</td>
<td>Seizure disorder, anorexia, bulimia, use of MAOI in 14 days, patients undergoing abrupt discontinuation of alcohol, sedatives and benzodiazepines</td>
<td>Depression, suicidal ideation, schizophrenia, bipolar other major depressive disorders</td>
</tr>
</tbody>
</table>
### 2.9 Management of Smoking Cessation

<table>
<thead>
<tr>
<th></th>
<th>Nicotine patch</th>
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<th>Bupropion</th>
<th>Varenicline</th>
</tr>
</thead>
</table>
| 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). |
| 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 (6-20 pieces/d) | $75-200 (6-20 pieces/d) | $175-350 (6-12 cartridges/d) | $100-250 (6-12 lozenges/d) | $60 | $125 |


**CANADIAN BEST PRACTICE RECOMMENDATIONS FOR STROKE CARE**

**CHAPTER 2: PREVENTION OF STROKE**

**REFERENCES**

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Clinical Practice Guidelines Related to the Prevention of Stroke


