CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

ACUTE STROKE MANAGEMENT:

PREHOSPITAL, EMERGENCY DEPARTMENT,

AND ACUTE INPATIENT STROKE CARE

Update 2018

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in collaboration with the Canadian Stroke Consortium
and the Canadian Association of Emergency Physicians

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Canadian Stroke Best Practice Recommendations

ACUTE STROKE MANAGEMENT: *PREHOSPITAL, EMERGENCY DEPARTMENT, AND ACUTE INPATIENT STROKE CARE*, SIXTH EDITION (UPDATED JUNE 2018)

Table of Contents

ACUTE STROKE MANAGEMENT: *PREHOSPITAL, EMERGENCY DEPARTMENT, AND ACUTE INPATIENT STROKE CARE*, SIXTH EDITION (UPDATED APRIL 2018)

PART ONE: INTRODUCTION AND OVERVIEW

I. Introduction to the Canadian Stroke Best Practice Recommendations

The *Canadian Stroke Best Practice Recommendations* (CSBPR) are intended to provide up-to-date evidence-based guidelines for the prevention and management of stroke, and to promote optimal recovery and reintegration for people who have experienced stroke (patients, families and informal caregivers). The CSBPR are under the leadership of the Heart and Stroke Foundation, Canada. They are intended for use by all members of the interdisciplinary teams that together care for stroke patients across the continuum from symptom onset to long term recovery. These best practice recommendations address issues relevant to all stroke types, including acute ischemic stroke, transient ischemic attack, intracerebral hemorrhage and subarachnoid hemorrhage.

The theme of the Sixth Edition of the CSBPR is ***Partnerships and Collaborations***. This theme stresses the importance of integration and coordination of partners across the healthcare system to ensure timely and seamless care of stroke patients to optimize recovery and outcomes. Working with people who have experienced a stroke, their family, friends and caregivers, interdisciplinary stroke experts, emergency medical services, other vascular care groups, community care providers, educators health administrators, and researchers will strengthen our ability to reduce risk factor prevalence and mortality from stroke. This theme also includes consideration of people who experience stroke who may also have other healthcare issues or conditions; known as multi-morbidities who have complex medical needs requiring collaboration among different specialty areas. As well, this theme emphasizes the critical need for partnerships to support and improve access to quality stroke care in rural and remote settings.

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

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

The *Canadian Stroke Best Practice Recommendations* are developed and presented within a continuous improvement model and are written for health system planners, funders, administrators, and healthcare professionals, all of whom have important roles in the optimization of stroke prevention and care and who are accountable for results. A strong stroke research literature base is drawn upon to guide the optimization of stroke prevention and care delivery. Several implementation tools are provided to facilitate uptake into practice, and are used in combination with active professional development programs. By monitoring performance, the impact of adherence to best practices is assessed and results then used to direct ongoing improvement. Recent stroke quality monitoring activities have compelling results which continue to support the value of adopting evidence-based best practices in organizing and delivering stroke care in Canada.

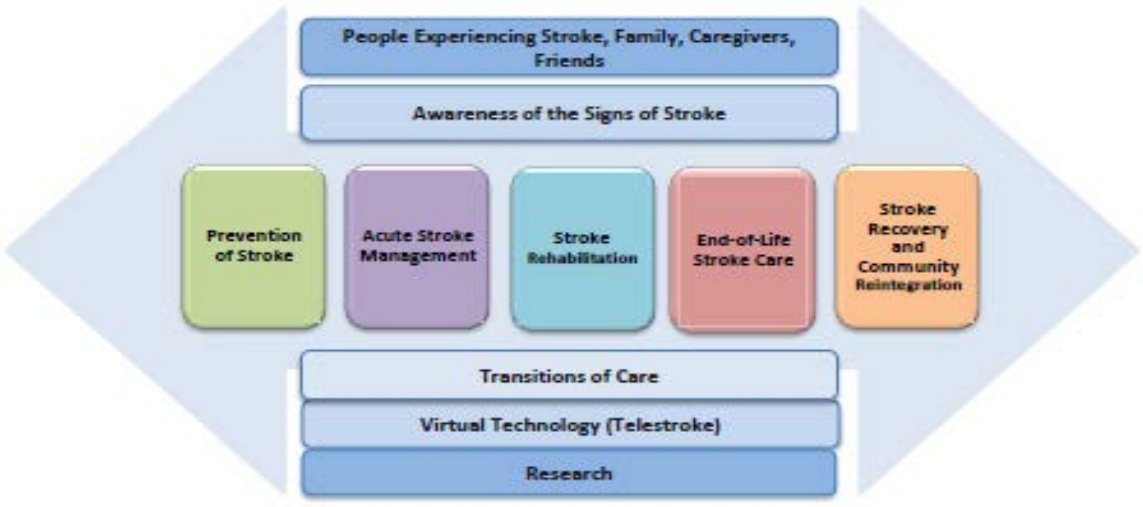
II. Profile of Stroke Care in Canada

- Every year, approximately 62,000 people with stroke and transient ischemic attack are treated in Canadian hospitals. Moreover, it is estimated that for each symptomatic stroke, there are approximately nine covert strokes that result in subtle changes in cognitive function and processes (Quality of Stroke Care in Canada Technical Report 2017, Heart and Stroke, based on CIHI DAD and NACRS data).
- Approximately 50,000 patients are admitted to acute care hospitals each year in Canada. (Quality of Stroke Care in Canada Technical Report 2017, Heart and Stroke, based on CIHI DAD and NACRS data).
- Stroke is the third leading cause of death in Canada and the second leading cause of death globally (CANSIM Table 2014, GBD 2017).
- Stroke is a leading cause of adult disability, with over 400,000 people in Canada living with the effects of stroke (Krueger 2015).
- The annual cost of stroke is approximately $3.6 billion, taking into account both healthcare costs and lost economic output (Krueger 2012).
- The human cost of stroke on families and communities is immeasurable.(Cameron 2017, Anderson 2017)

III. Acute Stroke Management Module Overview

The **Acute Stroke Management** module provides guidance to healthcare providers caring for people who present to the healthcare system with current or very recent symptoms of acute stroke or transient ischemic attack (TIA). This module also addresses the issue of public and healthcare provider's recognition of the signs of stroke and immediate actions to take, including contacting emergency medical services, arriving at a stroke – enabled emergency department, and launching local healthcare institution code stroke protocols. It represents care at the outset and in the middle of the stroke continuum (Figure 1). Stroke patients may move back and forth between different stages of care as their healthcare needs and situation changes.

Figure 1: Stroke Continuum of Care, 2018

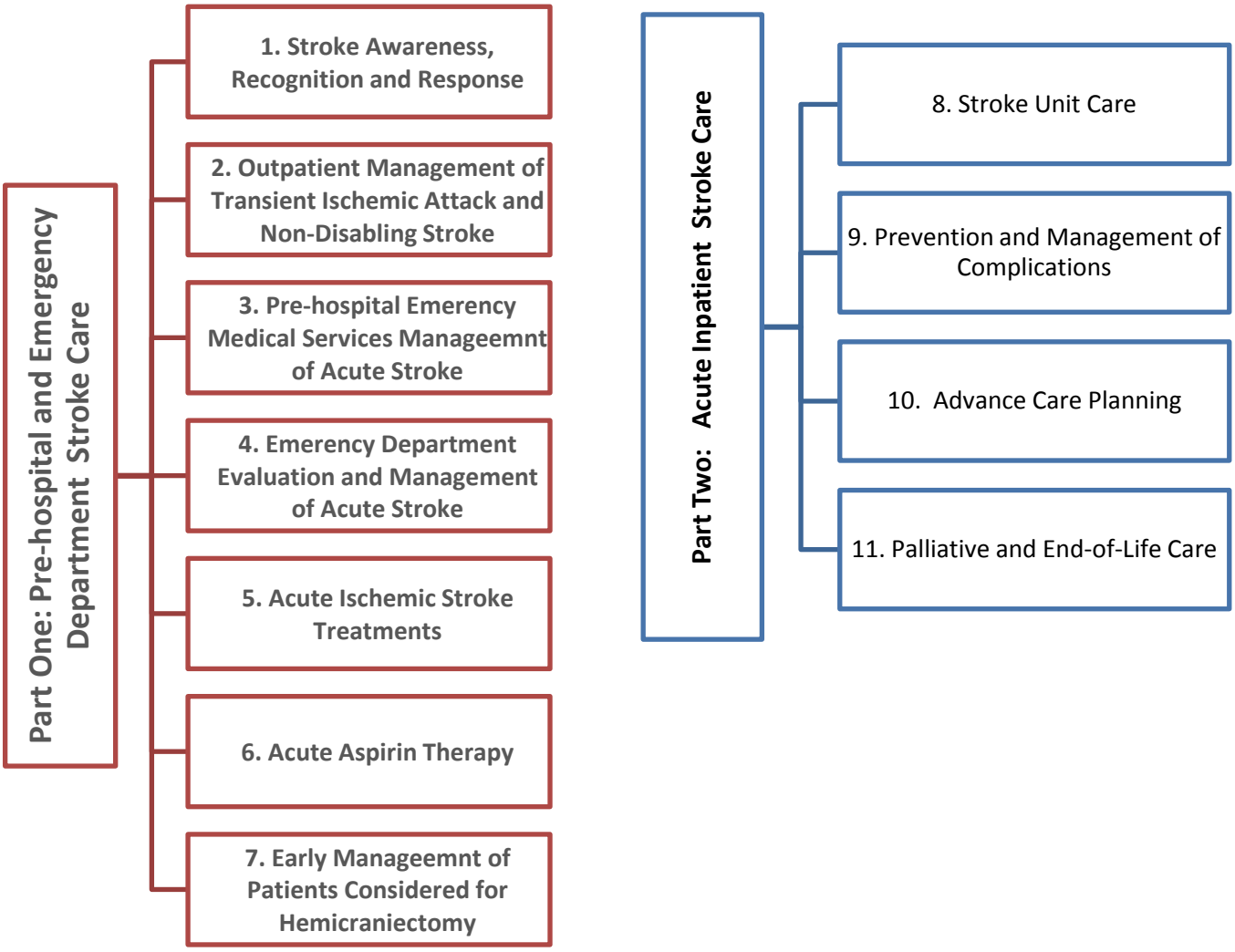


The **Acute Stroke Management** module provides guidance to healthcare providers caring for people who present to the healthcare system with current or very recent symptoms of acute stroke or transient ischemic attack (TIA). This module also addresses the issue of public and healthcare provider's recognition of the signs of stroke and immediate actions to take, including contacting emergency medical services, arriving at a stroke – enabled emergency department, and launching local healthcare institution code stroke protocols.

Prehospital and Emergency Department stroke care (Sections 1 – 7) involves all direct care, investigations, interventions, service delivery and interactions from first contact with the healthcare system after the onset of an acute stroke or transient ischemic attack – usually through contacting emergency medical services, or presenting at a healthcare facility – through to discharge from an emergency department to either another healthcare facility (usually with a higher or lower level of stroke care available), to an acute inpatient care unit or return to the community. The first four sections in the Acute Stroke Management module are applicable to all potential stroke patients arriving to hospital, sections five and six are specific to people experiencing an acute ischemic stroke, and section seven is applicable to all stroke patients.

Acute Inpatient Stroke Care (Sections 8 – 11) involves all direct care, investigations, interventions, service delivery and interactions occurring during the time a person who has had a stroke is admitted within an acute care hospital.

Figure 2: Acute Stroke Management Content, 2018



More detailed information regarding the care of people experiencing a hemorrhagic stroke – both intracerebral hemorrhage and subarachnoid hemorrhage – can be found in the Canadian Stroke Best Practices Hemorrhagic Stroke Module, which will be released in the fall of 2018.

IV. Acute Stroke Management Definitions

Acute Stroke: An episode of symptomatic neurological dysfunction caused by focal brain, retinal or spinal cord ischemia or hemorrhage with evidence of acute infarction or hemorrhage on imaging (MR, CT, retinal photomicrographs), and regardless of symptomatic duration.

Transient Ischemic Attack (TIA): A brief episode of neurological dysfunction caused by focal brain, spinal cord or retinal ischemia, with clinical symptoms and without imaging evidence of acute infarction. Transient ischemic attack and minor stroke are the mildest form of acute ischemic stroke in a continuum that cannot be differentiated by symptom duration alone, but the former typically resolves within one hour.

Prehospital and Emergency Department stroke care refers to the key interventions involved in the assessment, diagnosis, stabilization and treatment in the first hours after stroke onset. This represents all pre-hospital and initial emergency care for TIA, ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage and acute venous sinus thrombosis. This stage involves rapid triaging of patients based on stroke acuity and brain imaging. Treatments may include acute intravenous thrombolysis or acute endovascular interventions for ischemic stroke, emergency neurosurgical procedures, and same-day TIA diagnostic and risk stratification evaluation.

The principal aim of this phase of care is to diagnose the stroke type, and to coordinate and execute an individualized treatment plan as rapidly as possible.

Prehospital and Emergency care is time-sensitive by nature, minutes for disabling stroke and hours for TIA, but specific interventions are associated with their own individual treatment windows. Broadly speaking, the "hyperacute" time window refers to care offered in the first 24 hours after an acute stroke (ischemic and hemorrhagic) and the first 48 hours after a transient ischemic attack.

Acute stroke care refers to the key interventions involved in the assessment, treatment or management, and early recovery in the first days after stroke onset. This will represent all of the initial diagnostic procedures undertaken to identify the nature and mechanism of stroke, interdisciplinary care to prevent complications and promote early recovery, institution of an individualized secondary prevention plan, and engagement with the stroke survivor and family to assess and plan for transition to the next level of care (including a comprehensive assessment of rehabilitation needs). New models of acute ambulatory care such as rapid assessment TIA and minor stroke clinics or day-units are also starting to emerge.

The principal aims of this phase of care are to identify the nature and mechanism of stroke, prevent further stroke complications, promote early recovery, and (in the case of severest strokes) provide palliation or end-of-life care.

Broadly speaking "acute care" refers to the first days to weeks of inpatient treatment with stroke survivors transitioning from this level of care to either inpatient rehabilitation, community based rehabilitation services, home (with or without support services), continuing care, or palliative care. This acute phase of care is usually considered to have ended either at the time of acute stroke unit discharge or by 30 days of hospital admission.

V. Notable Changes in the Acute Stroke Management Module, Update 2018

With each update edition of the *Canadian Stroke Best Practice* modules, the most current evidence on the included topics are reviewed by the writing group members and internal and external reviewers. Recommendations from the previous edition may be continued unchanged, modified to reflect updated evidence (either wording or evidence levels), or removed. New recommendations may be added to address emerging evidence and practice changes.

- For the Sixth Edition, the module on Prehospital and Emergency Department Stroke Care, and the module on Acute Inpatient Stroke Care have been combined into one comprehensive *Acute Stroke Management: Prehospital, Emergency Department and Inpatient Stroke Care* Module.
- Sections addressing hemorrhagic stroke in previous editions of the Prehospital and Emergency Stroke Care module have been removed and will be included in a dedicated hemorrhagic stroke module, to be released in the fall of 2018.
- Note, a stroke cannot be classified as ischemic or hemorrhagic until initial braining imaging has been completed, therefore Sections 1 – 4 in the Prehospital and Emergency Department Stroke Care module apply to all patients with stroke signs and symptoms.

Updates to the Prehospital and Emergency Department Stroke Care Section, 2018

The following list highlights more notable changes for this 6th edition of the Prehospital and Emergency Stroke Care module:

- The sections on emergency management of intracerebral hemorrhage and subarachnoid hemorrhage have been removed from this module. A new module will be released in late 2018 that focus on assessment, diagnosis and management of hemorrhagic stroke across the continuum of care.
- Revisions to the recommendations for the triage and assessment of risk of recurrent stroke after TIA/minor stroke and suggested urgency levels for investigations and initiation of management strategies (Section 2);
- For Emergency Medical Services, a two-step screening has been recommended for paramedics: first to determine presence of stroke signs and symptoms, then a second screen for severity of presenting symptoms using validated scales (Section 3);
- The management of blood pressure in the first hours following stroke has been updated to address recent evidence (Section 4);
- Updates and clarity for recommendations have been made with respect to initial imaging in the emergency department – all imaging recommendations have now been consolidated into Section 4;
- New clinical considerations for treating a highly selected group of people with stroke of unknown time of onset with presentation beyond the 4.5 hour time window which incorporates findings from WAKE-UP (Thomalla et al, 2018) (Section 5.1);
- Updates to endovascular thrombectomy treatment recommendations and time windows based on emerging evidence have been completed (Section 5.5);
- Revised section on acute antiplatelet therapy with new and updated recommendations for dual antiplatelet therapy for a limited duration after acute minor ischemic stroke and TIA incorporating the findings from POINT (Johnston et al, 2018) (Section 6).

Updates to the Acute Inpatient Stroke Care Section, 2018

The following list highlights more notable changes for this 6th edition of the Acute Inpatient Stroke Care module:

- All recommendations related to intracerebral hemorrhage and subarachnoid hemorrhage have been removed, and will be included in a new module dedicated to hemorrhagic stroke (for release Fall 2018);

- Revisions to recommendations for care of patients experiencing stroke while already in hospital for other causes (Section 8);
- Updates to early mobilization recommendations based on newer evidence from the AVERT trials sub-analyses and cohort studies (Section 9);
- Moderate revisions to advanced care planning and palliative and end-of-life care recommendations (Sections 10 and 11 respectively).

VI. Guideline Development Methodology

The *Canadian Stroke Best Practice Recommendations* present high-quality, evidence-based stroke care guidelines in a standardized framework to support healthcare administrators and professionals across all disciplines. Implementation of these recommendations is expected to reduce practice variations and closing the gaps between evidence and practice.

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

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

1. The establishment of expert interdisciplinary writing group for each module, with the inclusion of stroke survivors and/or caregivers (Appendix One).
2. A systematic search, appraisal and update of research literature up to March 2018.
3. A systematic search and appraisal of external reference guideline recommendations.
4. The update of evidence summary tables.
5. Writing group review and revision of existing recommendations, with the development of new recommendations as required.
6. Submission of proposed chapter update to the Canadian Stroke Best Practices Advisory Committee.
7. Internal review of proposed chapter update. Feedback to writing group, completion of edits.
8. External review, and final edits based on feedback. (List of external reviewers included in Appendix One).
9. Update of educational materials and implementation resources.
10. Final approvals, endorsement and translation of chapter.
11. Public release & dissemination of final chapter update.
12. Continue with ongoing review and update process.

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

Conflicts of Interest: All potential participants in the recommendation development and review process are required to sign confidentiality agreements and to declare all actual and potential conflicts of interest in writing. Any conflicts of interest that are declared are reviewed by the Chairs of the Best

Practices Advisory Committee and appropriate HSF staff members for their potential impact. Potential members of any writing group who have conflicts that are considered to be significant are not selected for advisory or writing group. Participants who have conflicts for one particular topic area are identified at the beginning of discussions for that topic, and if it is the chair, then another non-conflicted participant assumes the chair role for that discussion to ensure balanced discussions. Declarations of Conflict of Interest for writing group members can be found in **Appendix One.**

Assigning Evidence Levels: The writing group was provided with comprehensive evidence tables that include summaries of all high quality evidence identified through the literature searches. The writing group discusses and debates the value of the evidence and through consensus develops a final set of proposed recommendations. Through their discussions, additional research may be identified and added to the evidence tables if consensus on the value of the research is achieved. All recommendations are assigned a level of evidence ranging from A to C, according to the criteria defined in Table 1. When developing and including "C-Level" recommendations, consensus is obtained among the writing group and validated through the internal and external review process. This level of evidence is used cautiously, and only when there is a lack of stronger evidence for topics considered important system drivers for stroke care (e.g., transport using ambulance services or some screening practices). An additional category for Clinical Considerations has been added for the Sixth Edition. Included in this section are expert opinion statements in response to requests from a range of healthcare professionals who seek guidance and direction from the experts on specific clinical issues faced on a regular basis in the absence of any evidence on that topic.

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

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

* (adapted from Guyatt et al. 2008 and Hypertension Canada 2017) [12]

VII. Acknowledgements, Funding, Citation

Acknowledgements

Heart and Stroke gratefully acknowledges the Acute Stroke Management writing group leaders and members all of whom have volunteered their time and expertise to the update of these recommendations. Members of the Canadian Stroke Consortium were involved in all aspects of the development of these recommendations. Members of the Canadian Association of Emergency Physicians were involved in the development of recommendations relevant to their practice, and included: Alix Carter, Crystal Doyle, Charles Duffy, Nadder Sharif, Kevin Lobay, Bilal Mir, Amani Otoom, Jeffrey J Perry, Anthony Shearing, and Etienne van der Linde. We acknowledge and thank Randy Mellow, President, and Kelly Nash, Executive Director of the Paramedic Chiefs of Canada, and their members who collaborated, reviewed and provided suggestions for this document. Jeffrey Myers and Moira Teed provided review for sections of this module. Mayank Goyal and Bijoy Menon provided input on early drafts of the recommendations. Norine Foley, Sanjit Bhogal and the evidence analysis team at workHORSE provided all evidence extraction and synthesis. These recommendations underwent external review by Marie-Christine Camden, Adrian Fawcett, Neala Gill, M. Shazam Hussain, Pooja Khatri, Timo Krings, Ariane Mackey, Antonia Nucera, Rhonda McNicoll – Whiteman, Thanh Nguyen, Catherine Patocka, Jeremy Rempel, Danielle Roy, Sean Sopher, Joseph Silvaggio, Neil E. Schwartz. These recommendations were reviewed and approved by the Heart & Stroke Canadian Stroke Best Practices and Stroke Quality Advisory Committee members, including Eric Smith, Ed Harrison, Robert Cote, Andrew Demchuk, Denyse Richardson, Alexandre Poppe, Moira Kapral, Farrell Leibovitch, Christine Papoushek, Alan Bell, Barbara Campbell, Cassie Chisholm, Hillel Finestone, Dwayne Forsman, Devin Harris, Michael Hill, Thomas Jeerakathil, Michael Kelly, Noreen Kamal, Eddy Lang, Beth Linkewich, Colleen O'Connell, Jai Shankar, Mike Sharma, Dawn Tymianski, Katie White, and Samuel Yip. Support and contributions to the development and publication of these recommendations was provided by internal Heart and Stroke teams including communications, translation, knowledge exchange, promote recovery, health policy and digital technology.

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Citing the Acute Stroke Management Module Update 2018 (Sixth Edition):

Boulanger JM (First Author), Lindsay MP (Corresponding Author), Stotts G, Gubitz, G, Smith EE, Foley N, Bhogal S, Boyle K, Braun L, Goddard T, Heran MKS, Kanya-Forster N, Lang E, Lavoie P, McClelland M, O'Kelly C, Pageau P, Pettersen J, Purvis H, Shamy M, Tampieri D, vanAdel B, Verbeek R, Blacquiere D, Casaubon L, Ferguson D, Hegedus J, Jacquin GJ, Kelly M, Linkewich B, Mann B, Milot G, Newcommon N, Poirier P, Simpkin W, Snieder E, Trivedi A, Whelan R, Smitko, E, Butcher K (Senior Author). On behalf of the *on Behalf of the Acute Stroke Management Best Practice Writing Group, and the Canadian Stroke Best Practices and Quality Advisory Committees; in collaboration with the Canadian Stroke Consortium and the Canadian Association of Emergency Physicians. In Lindsay MP, Gubitz G, Dowlatshahi D, Harrison E, and Smith EE (Editors) on behalf of the Canadian Stroke Best Practices Advisory and Quality Committees. Canadian Stroke Best Practice Recommendations, 2018; Ottawa, Ontario Canada: Heart and Stroke Foundation*.

The recommendations included in this module are also published in the International Journal of Stroke:

http://journals.sagepub.com/doi/full/10.1177/1747493018786616

Comments

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

Please forward comments to the Canadian Stroke Best Practices Team at Heart and Stroke: strokebestpractices@heartandstroke .ca.

CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS, SIXTH EDITION

PART TWO: PREHOSPITAL AND EMERGENCY STROKE CARE RECOMMENDATIONS

Section One: Stroke Awareness, Recognition and Response (Sixth Edition, 2018)

1. Stroke Awareness, Recognition and Response Recommendations

i. All members of the public and all healthcare providers should be educated that stroke is a medical emergency [Evidence Level C].

ii. Public and healthcare provider education should focus on recognizing the signs and symptoms of stroke and actions to take when experiencing or witnessing the signs of stroke [Evidence Level C]. *Refer to Box 1A below.*

iii. Public awareness campaigns and education should include use of the FAST (Face, Arms, Speech, Time) acronym to facilitate memory and recognition of these signs [Evidence Level B]. *Refer to Box 1A below.*

iv. Public and healthcare provider education should emphasize the need to respond immediately by calling 9-1-1 or their local emergency number [Evidence Level B], even if symptoms resolve.

   a. The public should be prepared to provide relevant information and answer questions from the dispatcher, paramedics and others [Evidence Level C]. *Refer to Box 1B below.*

   b. The public should be aware of the importance of following instructions of the emergency medical system dispatch centre [Evidence Level C].

v. Public and healthcare provider education should include information that stroke can affect persons of any age including newborns, children and all adults. Education should also emphasize the benefits of early emergency treatment [Evidence Level B]. *Refer to Rationale for details of early benefits.*

For recommendations on Emergency Medical Services and Pre-Hospital Care, refer to Section 3.

Rationale

When it comes to stroke, *time is brain!* On average, two million neurons die with every minute that elapses following symptom onset, leading to permanent damage to the brain (Saver 2009).

Stroke is a medical emergency. Many people do not recognize the signs and symptoms of stroke or attribute the signs to a less serious health issue and therefore do not seek immediate medical attention. It is critical that all people with strokes arrive in the emergency department as soon as possible, as earlier assessment and treatment may allow time for life-saving intervention. People who experience a transient ischemic attack (TIA) are also considered a medical emergency and require rapid assessment and treatment.

Efforts to enhance emergency medical system response for people having a stroke and to encourage the public to recognize stroke signs and symptoms and contact emergency medical services result in quicker treatment and better outcomes.

These recommendations apply across all geographic regions, and education should apply uniformly, with targeted approaches for diverse population groups, regardless of local issues related to time to access care.

System Implications

1. Government funding and support for awareness initiatives to improve the recognition and recall of the signs of stroke (e.g. FAST – a global best practice) and the importance of contacting 9-1-1 immediately. Awareness and education campaigns should be tailored to the cultural and language preferences of various population segments to ensure better uptake and understanding.
2. Enhanced collaboration among community organizations and healthcare professionals to ensure consistency in public education of the signs of stroke with a strong emphasis on the urgency of responding when the signs of stroke are recognized.
3. Training and education for emergency medical services, medical and nursing students, physicians in primary and acute care as well as specialists, nurses and allied health professionals to increase ability to recognize potential stroke patients and provide rapid assessment and management.
4. Comprehensive systems in place to ensure all people in Canada have access to timely and appropriate emergency medical services including ambulatory services without financial burden and quality stroke care regardless of geographic location.
5. To monitor and improve awareness among all people in Canada, healthcare systems, provincial/territorial and federal governments should generate linked health and social surveillance data and use it to drive quality improvement through better understanding of the health and social issues facing people in Canada

Performance Measures

1. Proportion of the population (and specific population subgroups) aware of the signs of stroke as presented in FAST *(core).*
2. Proportion of people with stroke or TIA transported to acute care by paramedics (core).
3. Median time (hours) from stroke symptom onset to arrival at an emergency department.
4. Proportion of patients who seek medical attention within 4.5, 6 and 24 hours of stroke symptom onset (core).
5. Median (IQR) time lapse between stroke symptom onset and first contact with emergency medical services defined as time call placed to 9-1-1 or local emergency medical system dispatch.
6. Proportion of the population who live within 4.5 and 6 hours by ground transportation of a hospital equipped to provide hyperacute stroke care (i.e., has CT scanner onsite and ability to deliver alteplase).

Refer to Section 3 for additional performance measures related to pre-hospital care and transport.

Measurement Notes

a. Performance measure 1: data may be obtained from specific public polling on the signs of stroke, by the Heart and Stroke Foundation, and other organizations.
b. Performance measures 2 – 4: Data may be obtained from the Canadian Institute of Health Information NACRS and DAD databases and Stroke Special Project 340 and/or from primary chart audit.
c. Performance measure 3 – ED triage time should always be used as the proxy time for ED arrival, and this is available in CIHI NACRS, and a calculated value in the DAD. The three time windows reflect the treatment times in this updated edition of the Acute Stroke Management Recommendations.

d. Performance measures 3 and 4: Stroke symptom onset may be known if the patient was awake and conscious at the time of onset, or it may be unknown if symptoms were present on awakening. It is important to record whether the time of onset was estimated or exact. The time qualifies as exact provided that (1) the patient is competent and definitely noted the time of symptom onset or (2) the onset was observed by another person who took note of the time.
e. Performance measure 6 may be obtained by performing geo-spatial analysis based on location of ambulance base stations, location of hospitals with hyperacute stroke services and road geography for a specified region.

Implementation Resources and Knowledge Transfer Tools

Health Care Provider Information

- Heart and Stroke Foundation FAST webpage at www.heartandstroke.ca/fast
- Canadian Stroke Best Practices FAST Educational Slide Presentation, available by request strokebestpractices@hsf.ca
- World Stroke Organization: http://www.world-stroke.org/
- Heart and Stroke Critical Steps in Early Stroke Management Resource

Patient Information

- Heart and Stroke Foundation FAST webpage at www.heartandstroke.ca/fast
- Your Stroke Journey (available) www.heartandstroke.com
- A Family Guide to Pediatric Stroke, available at http://www.strokebestpractices.ca/wp-content/uploads/2011/10/PEDSGuide-EN.pdf
- Stroke in Young adults: a resource for patients and families available at http://www.canadianstroke.ca/wp-content/uploads/2014/12/Stroke_Young_FINAL.pdf

Summary of the Evidence 2018

The results from many cross-sectional surveys indicate that, among members of the general public, knowledge of the signs and symptoms associated with stroke is poor. Failure of recognition on the part of either those witnessing a stroke or the person experiencing a stroke event can delay the time to contact emergency services, which may in turn decrease a patient's opportunity to receive time-sensitive treatment. Mochari-Greenberger et al. (2014) surveyed 1,205 women aged ≥25 years living in the United States who had participated in the American Heart Association National Women's Tracking Survey. Participants were contacted by telephone and asked standardized questions related to stroke warning signs and actions to take in the event of stroke. Sudden weakness and/or numbness of the face or limb of one side were the most commonly-cited symptom (51%). Loss of/trouble with understanding speech was also frequently recognized as a symptom (44%), while headache, unexplained dizziness and loss of vision in one eye were only recognized by 23%, 20% and 18% of respondents, respectively. One in 5 women could not name any of the stroke warning signs. Lundelin et al. (2012) conducted telephone surveys of 11,827 adults living in Spain who had participated in the Study on Nutrition & Cardiovascular Risk in Spain study to assess their ability to identify stroke symptoms, including sudden confusion or trouble speaking, numbness of face, arm or leg, sudden trouble seeing in one or both eyes, sudden chest pain (decoy), sudden trouble walking, dizziness or loss of balance and severe headache. 65.2% of the participants could correctly identify 4-6 symptoms of stroke, although only 19% could identify all 6 symptoms correctly and 11.4% were unable to identify a single symptom. 81.1% of participants indicated that they would call an ambulance if they suspected someone was having a stroke. Persons who could identify more stroke symptoms were more likely to call for an ambulance.

Even after an individual has suffered a stroke, they may remain unaware of stroke risk factors, including their own. Of 195 patients admitted to hospital following a confirmed stroke or TIA, a high percentage could not identify their own stroke risk factors (Soomann et al. 2015). Diabetes was the best recognized risk factor (89%), while 78% and 77% of patients were aware of atrial fibrillation and previous stroke, respectively. Sundseth et al. (2014) reported that among 287 patients admitted to hospital with a suspected stroke or TIA, 43.2% were able to name at least one stroke risk factor, while 13.9% could identify two and 1.7% knew three. Smoking and hypertension were the two most commonly cited risk factors for stroke. In terms of their knowledge of the signs and symptoms of stroke, 70.7% of patients knew at least one symptom of stroke. 66.6% identified numbness or weakness of the face, arm or leg, 45.6% identified confusion or trouble speaking or understanding speech, while 42.9% patients were able to identify both symptoms.

The number of public awareness campaigns designed to increase the recognition of the signs and symptoms of stroke has increased over the past decade. One of the most recognized programs is FAST, a mnemonic standing for F-face drooping, A-arm weakness, S-speech difficulties and T-time to call 911. The results of several studies evaluating the effectiveness of these campaigns indicates that exposure is associated with increased awareness of the signs and symptoms of stroke. Bray et al. (2013) surveyed 12,439 individuals ≥40 years of age from the general population in Australia and reported that from 2004 to 2010 there was a significant increase in the number of respondents who were aware of the national multimedia stroke awareness campaigns (31% vs 50%), which included FAST. The authors also reported an increase in the number of participants able to name ≥1 (69% vs 81%), ≥2 (43% vs 63%), and ≥3 (19% vs 32%) warning signs of stroke. Respondents who could identify ≥2 warning signs were significantly more likely to be aware of the campaign (OR=1.88, 95% CI 1.74 to 2.04). Similar results were reported from a Swedish mass-media campaign (Nordanstig et al. 2017), whereby the number of respondents who could identify some, or all of the words in the FAST mnemonic increased significantly from 4% before the campaign, to 23% during and immediately after, although decreasing to 14%, 21 months after the campaign ended. Jurkowski et al. (2010) reported that following a public awareness campaign to increase awareness of FAST, respondents who were exposed to a 3-phase multimedia campaign over a 7-month period were more likely to be aware of the campaign and its primary message to call 9-1-1. From pre- to post-campaign, the percentage of respondents who reported they would call 9-1-1 in response to specific stroke symptoms increased from 9%-12% for specific symptoms identified in oneself and 4%-12% for specific symptoms identified in others, compared to those who had not been exposed to the campaign.

Rasura et al. (2014) conducted a review of 22 studies, of which 14 targeted the general public using mass media campaigns. The duration of these campaigns varied from 3 months to 4 years. Three popular stroke signs and symptoms were included in all of the studies using mass media campaigns: FAST, SUDDEN and Give-Me-Five. Effectiveness of the interventions was assessed in most studies through questionnaires administered pre-and post-intervention. The authors concluded that large public health campaigns using mass media are expensive and short lived and may not be effective, although the increased costs could be mitigated through more prompt treatment with t-PA. They also indicated that, to be effective, the message being delivered must direct the person to call an ambulance. They also reported that the dose of the campaign appeared to be as important as the message. Television was found to be the most effective medium. While online campaigns can also be successful, the authors reported that they tend to attract a self-selected group (e.g. well-educated women).

Mass media campaigns have also been shown to be associated with increases in the use of thrombolytic agents following acute stroke. Advani et al. (2016) reported that the average number of

patients treated with t-PA increased significantly from 7.3 to 11.3 patients per month (an increase of 54.7%, p=0.02) in the 6-month period following the introduction of a mass media intervention that featured the FAST mnemonic, compared to the preceding 12 month-period. The average number of patients treated in the ER increased significantly from 37.3 to 72.8 patients per month (an increase of 95.7%, p<0.001) during the same period. Although the mean number of patients treated with t-PA dropped to 9.5 per month after the first 6 months of the campaign, it was still significantly higher than the preceding 12 months. In a telephone survey including 1,400 participants, the number of people who could name any stroke symptom increased from 66% to 75%. Of those who could name a symptom, 52% recognized facial droop, 42% named speech difficulties and 42% named arm weakness.

Reference List and Evidence Tables

Stroke Recognition and Response Evidence Tables and Reference List

Box 1A: Signs of Stroke - FAST

Heart & Stroke , www.heartandstroke.ca/fast

Box 1B: Core Information Required by Dispatch, Paramedics and Receiving Healthcare Facility

- Where permitted, limited identifiers such as name, date of birth and/or health card number be provided in order to expedite the registration process.
- Location of patient
- Signs of stroke apparent and visible in patient – including face, arm, speech involvement
- Signs of stroke onset time if witnessed, and last seen well time if not witnessed
- Current condition of the patient having a stroke, and changes in their condition since the stroke symptoms started
- Current medications if known
- Additional health problems, if known

- Collect phone number of witness to verify information
- Advanced care directives if available

Refer to Section 3 for additional information related to pre-hospital care and transport.

Section Two: Outpatient Management of TIA and Non-Disabling Stroke (Sixth Edition, 2018)

2. Outpatient Management of TIA and Non-Disabling Stroke

NOTES on this recommendation

Ideally, people experiencing any of the signs of an acute stroke should immediately go to an emergency department.

Unfortunately, this is not always the case; the reality is that some people experiencing signs of acute stroke may present to an outpatient setting such as a primary care physician or family health team office, community clinic, or urgent care centre.

People experiencing signs of stroke require rapid assessment, diagnosis and determination of risk for a recurrent stroke. Patients determined to have transient ischemic attack, or subacute, nondisabling ischemic stroke who are not candidates for hyperacute treatment with intravenous alteplase (tPA) or endovascular thrombectomy may then be prioritized for secondary prevention of stroke assessment and management. ***For these patients, please refer to the Secondary Prevention of Stroke Module***

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

2.1 Timing of Initial Assessment

(Please refer to Box 2A for summary of Stroke Risk Levels and Actions)

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

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

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

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

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

ii. Patients identified as highest risk should be ***immediately*** sent to an emergency department with capacity for advanced stroke care (such as brain imaging on site, and ideally access to acute stroke treatments) [Evidence Level C] *Refer to Section 2.2 for more information on investigations.*

iii. Urgent brain imaging (CT or MRI) and non-invasive vascular imaging (CT angiography (CTA) or MR angiography (MRA) from aortic arch to vertex) should be completed as soon as possible **within 24 hours** [Evidence Level B]. *Refer to Section 2.2 for more information on investigations*.

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

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

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

ii. These patients should receive a comprehensive clinical evaluation and investigations by a healthcare professional with stroke expertise as soon as possible [Evidence Level B]**, ideally initiated within 24 hours** of first contact with the healthcare system [Evidence Level C]. *Refer to Section 2.2 for more information on investigations.*

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

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

ii. These patients should receive a comprehensive clinical evaluation and investigations by a healthcare professional with stroke expertise as soon as possible [Evidence Level B], **ideally within 2 weeks** of first contact with the healthcare system [Evidence Level C]. *Refer to Section 2.2 for more information on investigations.*

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

i. Patients **presenting more than 2 weeks** following a suspected transient ischemic attack or nondisabling ischemic stroke, may be considered as being less urgent, and should be seen by a neurologist or stroke specialist for evaluation, **ideally within one month** of symptom onset [Evidence Level C]. *Refer to Section 2.2 for more information on investigations.*

2.2 Diagnostic Investigations

2.2.1 Initial Assessment:

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

   a. Brain imaging (CT or MRI) and non-invasive vascular imaging (CTA or MRA from aortic arch to vertex) should be completed as appropriate and within time frames based on triage category and severity described in Section 2.1 [Evidence Level B]. *Refer to Table 2A for additional information, and Section 4 for detailed recommendations on neuroimaging.*

   b. CTA including extracranial and intracranial vasculature from aortic arch to vertex, which can be performed at the time of initial brain CT, is recommended as an ideal way to assess both the extracranial and intracranial circulation [Evidence Level B].

      Note: Some facilities may not have CTA readily available and vascular imaging will need to be based on available resources and equipment.

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

d. Carotid ultrasound (for extracranial vascular imaging) and MR angiography are acceptable alternatives to CTA, and selection should be based on immediate availability, and patient characteristics [Evidence Level C].

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

a. **Initial bloodwork**: haematology (complete blood count), electrolytes, coagulation (aPTT, INR), renal function (creatinine, e-glomerular filtration rate), random glucose and troponin [Evidence Level C]. *Refer to Table 2B for full list of recommended lab tests.*

b. **Subsequent** laboratory tests may be considered during patient encounter or as an outpatient, including a lipid profile (fasting or non-fasting); and, screening for diabetes with either a glycated hemoglobin (HbA1c), or 75 g oral glucose tolerance test [Evidence Level C]. *Refer to Diabetes Canada Guidelines for further information*

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

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

Clinical Considerations:

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

2.2.2 Additional Investigations for Embolic Stroke of Undetermined Source (ESUS)

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

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

For recommendations on immediate clinical management with antiplatelet therapy, refer to section 6 in this module.

2.3 Functional Assessment:

i. Patients with transient ischemic attack or ischemic stroke should be assessed for neurological

impairments and functional limitations (e.g., cognitive evaluation, screening for depression, screening of fitness to drive, need for potential rehabilitation therapy, and assistance with activities of daily living) [Evidence Level B]. *Refer to Rehabilitation Module Recommendations 5.1 and 5.6 for additional information.*

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

Rationale

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

There is clear evidence that transient ischemic attacks or minor strokes are unstable conditions that warn of high future risk of stroke, other vascular events, or death. The risk of recurrent stroke after a transient ischemic attack has been reported as 12 to 20 percent within 90 days, and the risk is "front-loaded", with half of the strokes occurring in the first two days following initial symptom onset. The seven-day risk of stroke following a transient ischemic attack can be as high as 36 percent in patients with multiple risk factors. Timely initiation of secondary prevention medical therapy and carotid endarterectomy has been shown to significantly reduce the risk of major stroke after an initial transient ischemic attack or non-disabling stroke. A recent study by the TIARegistry.Org group reported updated rates that were less than half that expected from historical cohorts and could be explained by better and faster implementation of secondary stroke prevention strategies in this cohort through rapid-access TIA clinics. (Amarenco et al. **N Engl J Med 2016;374:1533-42)**

System Implications

1. Education for the public and healthcare providers (primary, acute and specialists) about the urgency of assessment and management of transient ischemic attack or non-disabling ischemic stroke is critical to reduce the risk of recurrent, potentially more serious events. Patients and families will also require ongoing education and support related to prevention and management of stroke and its associated risk factors.
2. Education and training for physicians who work in primary, secondary, and tertiary care settings, to enable the management of patients with transient ischemic attack or non-disabling ischemic stroke in a timely manner.
3. Processes, protocols and infrastructure in place to enable rapid access to diagnostic tests and expertise for patients with transient ischemic attack or minor stroke in community healthcare settings and acute healthcare facilities.
4. Well-established and accessible stroke prevention clinics or broader vascular prevention programs appropriately funded and available in all communities through traditional or technological means.
5. Universal access to necessary stroke prevention medicines like anti-hypertensives is critical to management and secondary prevention. Provincial and national systems should develop an equitable pharmaceutical strategy which improves access to cost effective medicines for all people in Canada, regardless of geography or ability to pay.
6. Promotion of programs with healthcare practitioners. These resources should be listed, easily accessible to primary care physicians and healthcare providers, and updated annually.
7. Monitoring, assessment and improvement of program regarding uptake, adherence and quality of stroke prevention programs to ensure patients can access effective services. Consideration should be given to community and individual barriers as well as motivators and enablers.

8. Any suspicion of ischemic stroke in a child warrants an emergent consult or assessment in a pediatric emergency department. All hospitals should have a referral process established with the closest specialized pediatric facility.

Performance Measures

1. Proportion of acute stroke and TIA patients who are discharged alive from an emergency department or an inpatient stay and then readmitted to hospital for any cause within 7 days and/or 14 days of index acute stroke discharge (KQI).
2. Proportion of patients with TIA or non-disabling stroke who are investigated and discharged from the emergency department who are referred to organized secondary stroke prevention services at discharge. (KQI)
3. Time from first encounter with medical care (primary care or emergency department) to assessment by a stroke expert (in clinic or other setting).
4. Proportion of patients with motor and speech TIAs or minor stroke who have CT head and CTA completed (or other vascular imaging) within 24 hours of presentation.
5. Time from first encounter with medical care to brain imaging (CT/MRI); vascular imaging (Doppler of cervical arteries, CT or MR angiography); and electrocardiogram.
6. ***Developmental KQI:*** *Proportion of HIGHEST risk TIA and non-disabling stroke patients who are investigated and managed within 24 hours in the ED or referred to organized secondary stroke prevention services (KQI)*

Measurement Notes

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

Implementation Resources and Knowledge Transfer Tools

Health Care Provider Information

- HSF Stroke Assessment and Prevention Pocket Cards 2017. Hard copy available through HSF order form
- HSF Stroke Assessment Pocket Cards http://www.strokebestpractices.ca/wp-content/uploads/2017/07/002-17_CSBP_StrokeAssessPocketGuide_7.5x4.25_EN_v6_LR.pdf
- Canadian Stroke Best Practice Recommendations PreHospital and Emergency Department Module: Table 2A: Recurrent Stroke Risk Levels and Initial Management
- Canadian Stroke Best Practice Recommendations PreHospital and Emergency Department Module: Table 2B: Recommended Laboratory Investigations for Patients with Acute Stroke or Transient Ischemic Attack
- Canadian Stroke Best Practice Recommendations PreHospital and Emergency Department Module: Appendix Three Screening and Assessment Tools for Acute Stroke Severity
- Canadian Cardiovascular Society Atrial Fibrillation Guidelines (Update 2016): http://www.onlinecjc.ca/article/S0828-282X(16)30829-7/fulltext
- American College of Chest Physicians (ACCP) Pulmonary Vascular Guidelines http://www.chestnet.org/Guidelines-and-Resources/CHEST-Guideline-Topic-Areas/Pulmonary-Vascular

- Canadian Association of Radiologists guidelines: https://car.ca/patient-care/practice-guidelines/
- Canadian Neurological Scale: https://www.strokengine.ca/assess/cns/

Patient Information

- Signs of stroke: http://www.heartandstroke.ca/stroke/signs-of-stroke
- Stroke information: http://www.heartandstroke.ca/stroke/what-is-stroke
- Atrial Fibrillation information: http://www.heartandstroke.ca/heart/conditions/atrial-fibrillation
- Your Stroke Journey: http://www.strokebestpractices.ca/wp-content/uploads/2015/03/YOURSTROKEJOURNEY.FINAL_.ENGLISH.pdf
- Post -Stroke Checklist: http://www.strokebestpractices.ca/wp-content/uploads/2014/06/HSF%20Post%20Stroke%20Checklist_WEB.pdf
- HSF Risk Factors for Heart Disease and Stroke (new 2017) http://www.heartandstroke.ca/-/media/pdf-files/iavc/health-information-catalogue/en-are-you-at-risk.ashx?la=en&hash=91D622380B55E55ADB31E7ECE37C9F51BCD26D9

Summary of the Evidence

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

Several clinical scales, such as ABCD and ABCD^2, have been developed for use by primary care and emergency department physicians to help guide triage decisions for patients presenting with possible TIA or minor stroke. While simple to apply, they may fail to identify patients with atrial fibrillation or significant carotid stenosis. The limitations of the ABCD^2 score were recently highlighted in a meta-analysis including the results of 29 studies (Wardlaw et al. 2015). In a hypothetical cohort of 1,000 unselected clinic referrals, the poor specificity of the scale (35.4%) resulted in a large number of stroke mimics being identified as high risk (i.e., ABCD^2 score ≥4). Rapid clinical assessment by stroke specialists and subsequent investigations to differentiate TIA and minor stroke from other potential causes are essential to ensure that secondary prevention strategies can be implemented as soon as possible. Urgent TIA clinics provide such a model of care. The TIAregistry.org project is a prospective registry designed to follow patients presenting with TIA or minor stroke over a 5-year period. Patients were included if the event had occurred within the previous 7 days. The preliminary one-year results, which included 4,583 patients recruited from 61 sites in 21 countries from 1997-2003, indicated that 78.4% of patients were seen by a stroke specialist within 24 hours of the event (Amarenco et al. 2016). Most patients received key urgent investigations before discharge and appropriate treatments were initiated. For example, 5.0% of patients received a new diagnosis of atrial fibrillation, of which 66.8% received anticoagulant therapy before discharge. Carotid stenosis of ≥50% was found in 15.5% of patients, of which 26.9% underwent

carotid revascularization before discharge. The one-year estimate of risk of the primary outcome, a composite of death from cardiovascular causes, nonfatal stroke and nonfatal acute coronary syndrome, was 6.2% (95% CI 5.5-7.0%). Estimates of the stroke rate at days 2, 7, 30, 90, and 365 were 1.5%, 2.1%, 2.8%, 3.7%, and 5.1%, respectively. These estimates were much lower than those compared with historical cohorts and were attributed to the widespread establishment of TIA clinics. Rothwell et al. (2007) reported that patients who had immediate access to a TIA clinic (EXPRESS) had a significantly reduced risk of recurrent stroke (2.1% vs.10.3%, p=0.0001), compared with an historical cohort who did not have immediate access to the same care. Patients with immediate access also received their prescriptions sooner (median of 1 vs. 20 days). Lavallée et al. (2007) reported the 90-day risk of stroke for all patients seen at their TIA-SOS clinic was lower than that predicted by their $ABCD^2$ score (1.24% vs. 5.96%).

Detecting atrial fibrillation (AF) after a stroke or TIA is important since it is a major risk factor for subsequent stroke and, once identified, can be effectively treated. However, AF is under-diagnosed because it is frequently paroxysmal and asymptomatic, and patients do not routinely undergo prolonged screening. The low levels of monitoring were highlighted in a study authored by Edwards et al. (2016). The records of 17,398 consecutive patients presenting with first-ever stroke or TIA with motor or speech deficits, without a known history of AF in sinus rhythm, were reviewed and the utilization of ambulatory ECG monitoring within the first 90 days of the event was assessed. A total of 5,318 patients (30.6%) received at least 24-hour Holter monitoring within 30 days of the index event. The numbers associated with more prolonged Holter monitoring were lower; 2,253 patients (12.9%) and 25 patients (0.1%) underwent 48-hr and >60-hr monitoring, respectively within 90 days. Monitoring with event loop recording was conducted in 139 patients (0.8%) within 90 days. A meta-analysis conducted by Sposato et al. (2015) examined the use of outpatient cardiac monitoring following minor stroke or TIA in 4 distinct phases. The results from the studies that initiated investigations during the second ambulatory period (phase 4), using mobile cardiac outpatient telemetry (n=5), external loop recording (n=7) or implantable loop recording devices (n=7), reported an estimated 16.9% (95% CI 13.0% -21.2%) of patients were diagnosed with AF.

The results from four RCTs and numerous observational studies have demonstrated that prolonged post-stroke ECG monitoring using wearable or insertable devices is effective for improving the detection of paroxysmal AF (number needed to screen range from 8-14), with longer monitoring durations associated with an increased probability of AF detection. In the Event Monitor Belt for Recording Atrial Fibrillation after a Cerebral Ischemic Event (EMBRACE) trail (Gladstone et al. 2014), a 30-day ambulatory cardiac event monitor was found to be superior to repeat 24-hour Holter monitoring in identifying AF in 572 patients aged 52 to 96 years (mean=72.5 years) without known AF, who had sustained a cryptogenic ischemic stroke or TIA within the previous 6 months. Atrial fibrillation lasting ≥30 seconds was detected in 16.1% of patients, using the cardiac event monitor compared with 3.2% of patients in the Holter group (absolute difference, 12.9%; 95% CI 8.0 to 17.6; p<0.001; number needed to screen= 8). The cardiac event monitor was also more likely to identify cases of AF lasting longer than ≥2.5 minutes (9.9% vs. 2.5%, absolute difference, 7.4%, 95% CI, 3.4 to 11.3; p<0.001). By 90 days, oral anticoagulant therapy had been prescribed for more patients in the intervention group (18.6% vs. 11.1%, p=0.01). Three-quarters of AF cases identified in the intervention group were detected within the first 2 weeks of monitoring. In a UK trial (Higgins et al. 2013) in which 100 patients with no history of AF and in sinus rhythm were randomized, a strategy of 7-day ECG monitoring in the acute phase post-stroke was found to be superior to standard care for the detection of paroxysmal AF (18% vs. 2%; p<0.05). Significantly more patients who received additional monitoring were started on anticoagulants.

The Finding Atrial Fibrillation in Stroke - Evaluation of Enhanced and Prolonged Holter Monitoring (FIND-AF) trial randomized 398 patients over age 60 years (average age 73 years) reported that a strategy of 10-day Holter monitoring started within the first week post stroke and repeated at 3 months and 6 months was superior to standard care, which consisted of an average of 73 hours of inpatient telemetry plus an

average of 24 hours of Holter monitoring (Wachter et al. 2016). At 6 months, detection of AF was significantly higher in the prolonged monitoring group (13.5% vs. 4.5%; absolute difference 9%, 95% CI 3.5-14.6, p=0.002; NNS=11). Similar findings were reported in the Cryptogenic Stroke and Underlying AF (CRYSTAL-AF) trial (Sanna et al. 2014) when patients (mean age of 61.5 years) received long-term monitoring with an insertable cardiac monitor (ICM). At 6 months, the rate of detection of AF was significantly higher among patients assigned to the ICM group (8.9% vs. 1.4%, HR=6.4, 95% CI 1.9-21.7, p<0.001), compared with those who received standard monitoring using ECG monitoring on a schedule at the discretion of their treating physician. Similar results were reported at 12 months (12.4% vs. 2.0%, HR=7.3, 95% CI 2.6- 20.8, p<0.001).

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

Laboratory investigations and assessment of physiological variables as part of a patient's initial evaluation provides important information for patient management. A small case control study found that maintenance of normal physiological variables within the first three days of stroke has a beneficial effect on outcomes post stroke (Langhorne et al. 2000). Blood biomarkers have been shown to correlate with cerebral lesion size and stroke severity (Kisialiou et al. 2012). Ferrari et al. (2010) found that hypertension, diabetes, possible etiology, acute infection and cardiac abnormalities were all independent predictors of deterioration following TIA or minor stroke, and recommended immediate diagnostic testing for their identification. Together, these findings suggest a complete evaluation of patients presenting with suspected stroke or TIA is beneficial for predicting risk of recurrent stroke and guiding patient management.

Reference List and Evidence Tables

Initial Triage and Evaluation Evidence Tables and Reference List

TABLE 2A: Summary of Canadian Stroke Best Practices Recurrent Stroke Risk Levels and Initial Management

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

Risk For Recurrent Stroke	Time from Stroke Symptom Onset to Healthcare Presentation	Presenting Symptoms	When Patients Should be Seen by Healthcare Professional	Where Patients Should be Seen	Tests to be Done on Initial Assessment
Very HIGH RISK	Within 48 hours	- Transient, fluctuating or persistent unilateral weakness (face, arm and/or leg) - Transient, fluctuating or persistent speech disturbance /aphasia. - Fluctuating or persistent symptoms **without motor weakness or language/ speech disturbance** (e.g. hemibody sensory symptoms, monocular visual loss, hemifield visual loss, +/- other symptoms suggestive of posterior circulation stroke such as diplopia, dysarthria, dysphagia, and / or ataxia).	Immediately	Emergency Department [ideally ED with brain imaging onsite and access to alteplase] or specialized high risk emergent clinic	CT/CTA or MRI/MRA (aortic arch to vertex), ECG, Lab Work (Table 2B)
HIGH RISK	Between 48 hours and 2 weeks	- Transient, fluctuating or persistent unilateral weakness (face, arm and/or leg), **or language/speech disturbance**	As soon as possible, ideally within 24 hours	Stroke Prevention Clinic with Neurologist or Stroke Specialist, Nurse Practitioner	CT/CTA or MRI/MRA (aortic arch to vertex), ECG, Lab Work (Table 2B)
Moderate (INCREASED) RISK	Between 48 hours and 2 weeks	- Fluctuating or persistent symptoms ***without motor weakness* or language/speech disturbance** (e.g., hemibody sensory symptoms, monocular vision loss, binocular diplopia, hemifield vision loss, dysarthria, dysphagia, and / or ataxia).	As soon as possible, ideally within 2 weeks	Stroke Prevention Clinic with Neurologist or Stroke Specialist, Nurse Practitioner	CT/CTA or MRI/MRA (aortic arch to vertex),* ECG, Lab Work (Table 2B) * Could consider carotid ultrasound if CTA not available
LOWER RISK	More than 2 weeks	- Any typical or atypical symptoms of stroke or transient ischemic attack	Ideally within 1 month	Ambulatory Clinic with access to Neurologist or Stroke Specialist, Nurse Practitioner	As appropriate based on assessment by healthcare team

Table 2B: Recommended Laboratory Investigations for Patients with Acute Stroke or Transient Ischemic Attack

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

Initial Recommended Laboratory Investigations for Patients with Stroke and TIA		
Complete Blood Count (CBC)	International Normalized Ratio (INR)	Partial Thromboplastin Time (PTT)
Random Glucose	Electrolytes	Creatinine with estimated glomerular filtration rate (eGFR)
Follow-up Blood work: to be completed as soon as possible after initial bloodwork	Glucose: Either a fasting plasma glucose or hemoglobin A1C, or 75 mg oral glucose tolerance test	Lipid profile (Fasting optional and decision should be based on individual patient factors)
	ALT	Troponin (based on clinical indications)

Additional Laboratory Investigations for Consideration in Specific Circumstances
Note: All patients are individual and some may require additional investigations to fully understand their clinical situation. The investigations noted below may not be indicated in many stroke patients and should be considered in selected stroke patients based on clinical presentation and medical history.

Optional Laboratory Investigations		
Calcium, Magnesium, Phosphate	If female less than 50 years of age, consider pregnancy test	Blood cultures x 3 (per individual institutional protocol)
Blood and/or urine drug screen	HIV, syphilis serology	
Coagulopathy Screen – For consideration in selected patients *only if clinically indicated* *Recommend consultation with a specialist in thrombosis to evaluate for hypercoagulable state*		
Anticardiolipin (Antiphospholipid) antibody, Beta 2 glycoprotein-1, Lupus anticoagulant	Sickle cell screen	Homocysteine (fasting serum level)
Special considerations especially in young adults and children with stroke in absence of identified etiology *(Note there is not a strong evidence base for these investigations, and they should be considered only in selected stroke patients based on clinical presentation and medical history*		
Consider LP for CSF analysis (cell count and differential, protein, glucose, bacterial and viral cultures; possibly cytology/flow cytometry if CNS lymphoma is a consideration)	Brain biopsy (if vasculitis of the central nervous system or angiocentric lymphoma is a consideration)	
Cerebral digital subtraction angiography	Further genetic tests if indicated – CADASIL, Fabry's, MELAS	

Section Three: Emergency Medical Services Management of Acute Stroke Patients (Sixth Edition, 2018)

3. Emergency Medical Services Management of Acute Stroke Patients Recommendations

Definitions and Context

Approximately two-thirds of all patients who seek acute care for stroke arrive at the emergency department by ambulance. Transport by paramedics is safer and enables patients to be triaged to appropriate hospitals that provide stroke services without delays. The current estimated target for transport to hospital by paramedics is in the range of 80% of cases (based on Canadian Stroke 2009 benchmark data).

Two timelines have been established to describe emergency medical services (EMS) in Canada for stroke patients who may be eligible for acute ischemic stroke therapy, including intravenous alteplase and endovascular thrombectomy. These are:

Timeline One: *The **pre-hospital phase** starts with symptom onset and ends with hospital arrival.** This includes on-scene management and transport time. Patients with ischemic stroke who can arrive at hospital and be treated as soon as possible within a **4.5 hour** time window from witnessed symptom onset (or when last seen well) may be eligible to receive medical treatment with intravenous thrombolysis; thrombolysis may be offered alone or in combination with endovascular thrombectomy which has a **6 hour** time window for most patients. Highly selected patients may be eligible for endovascular thrombectomy **up to 24 hours** from symptom onset. *Refer to Section 4, for more information.*

Timeline Two: *The **emergency department phase** starts with hospital arrival and ends with discharge from the emergency department decision time* – either with admission to a stroke unit or hospital ward for inpatient care or discharge to the community. This includes the diagnostic evaluation, consideration of treatment options, and initiation of treatment which should be completed in less than 60 minutes, initiation of treatment. Aim for a target 90th percentile for door-to-needle time of 60 minutes (upper limit); and a target median door-to-needle time of 30 minutes or less [Kamal et al CJNS 2015]. *Note, the goal is to transfer admitted stroke patients within four hours of arrival where possible; however, many hospitals operate at full capacity and patients may have to remain in the emergency department after they are admitted to inpatient care while waiting for an inpatient bed.*

It should be noted that the probability of disability-free survival decreases over time within the treatment window and all phases of patient care should aim for the shortest process and treatment times possible.

- These recommendations cover management of potential stroke patients between the time of first contact with the local emergency medical system to transfer of care to the hospital, as well as care of suspected or confirmed stroke patients who are being transferred between healthcare facilities by paramedics.
- These recommendations are directed to paramedics and those individuals who support emergency medical systems, including communications officers and dispatchers. It also applies to other first responders such as emergency medical responders and primary care paramedics who have been trained to screen for stroke and manage potential stroke patients during transfer.
- These recommendations are intended to be translated into practice by the entire breadth of out-of-hospital healthcare providers within the defined scope of practice of each. This includes emergency medical system professionals such as paramedics and emergency medical dispatchers, but also allied emergency medical system providers such as medical

first responders and emergency medical responders.

* ***Local variations should be taken into consideration for pre-hospital time (e.g., remote locations with poor road access).***

Recommendations

3.0 Out-of-hospital patient management should be optimized to meet the needs of suspected acute stroke patients, including recognition, management and rapid transport, usually done concurrently [Evidence Level C].

3.1 Access to Emergency Medical Services (EMS)

i. Immediate contact with emergency medical systems (e.g. 911) by people experiencing the signs of stroke, a witness or other members of the public is strongly recommended [Evidence Level B*]. Refer to Section 1 for additional information on Signs of Stroke.*

ii. **EMS Communications Centre**: All regions should implement a dispatch process through the EMS communications centre to recognize the probable stroke signs (such as FAST – Face, Arms, Speech), potential stroke diagnosis, and need for priority response to the scene and transport to a hospital capable of providing acute services for the rapid diagnosis and time-sensitive treatment of stroke (such as neuroimaging, and acute thrombolysis) [Evidence Level C].

iii. After dispatching the ambulance, it is recommended that emergency medical system communications centre personnel provide pre-arrival instructions to the person reporting the stroke (such as unlock door, move pets, determine stroke symptom onset time, determine current medications), in order to expedite and optimize pre-hospital care [Evidence Level C]. *Note, if the person experiencing the signs of stroke is the one to contact EMS, they may not be able to comply with these requests.*

3.2 Paramedic On-Scene Management

*Note: On-scene goal is to '**recognize and mobilize**' – it is of the utmost importance to proceed rapidly and safely to transport suspected stroke patients, as on-scene management for stroke patients is limited.*

i. EMS personnel should use validated acute stroke out-of-hospital diagnostic screening tools as part of on-scene assessment [Evidence Level B]. [New for 2018]

   a. Patients should be screened for **signs of stroke** using a validated stroke assessment tool that includes the components of FAST (Face, Arm, Speech, and Time) [Evidence Level B].

   b. Patients who demonstrate any FAST signs should then undergo a second screen using a tool validated to assess **stroke severity**, which may be considered in decisions for transportation destination [Evidence Level B]. [New for 2018] *Note: the purpose of this second screen is to look for possible EVT candidates, such as people exhibiting signs of cortical dysfunction (aphasia, visual changes, neglect).*

Refer to Appendix 2, Table 2A Canadian Stroke Best Practices Table of Standardized Acute Stroke Out-of-Hospital Diagnostic Screening Tools; Table 2B Glasgow Coma Scale, and Table 2C Canadian Stroke Best Practices Table of Pre-Hospital Stroke Severity Scales.

ii. It is recommended that EMS personnel obtain information from the patient, family members or other witnesses about the suspected stroke event (presenting symptoms, time of onset or time of symptom recognition or time last known well, and sequence of events), co-morbid conditions, current medications (especially anticoagulants), and any formal or informal advance directives that may influence care by EMS and in the emergency department [Evidence Level C].

iii. On-scene time with suspected stroke patients should be as short as possible; ideally a median time of 20 minutes or less* for patients who present within the 4.5-hour treatment time window

[Evidence level C]. *(* Target median of 20 minutes based on median EMS on-scene time data from across provinces contained in HSF Stroke Report 2015).*

iv. Initial assessment provided by paramedic's on-scene should include capillary blood glucose measurement [Evidence Level B].

v. Prior to transport, it is recommended that paramedics on-scene provide instructions to the patients' family, including recommending that the family/decision-maker accompany the patient to hospital or be accessible by phone for decision-making, as well as confirming time last known well, and providing required information about existing health conditions, current medications and other information as needed [Evidence Level C].

3.3 Transport of Suspected Stroke Patents

i. Direct transport protocols must be in place to facilitate the transfer of suspected acute stroke patients who are potentially eligible for thrombolytic and/or endovascular thrombectomy to the most appropriate acute care hospital capable of providing services for the diagnosis and treatment of acute stroke [Evidence Level C].

ii. It is recommended that direct transport protocol criteria be based on:

a. an EMS system set up to categorize patients exhibiting signs and symptoms of an acute stroke as a high priority for evaluation, response and transport [Evidence Level C];

b. the medical stability of the patient [Evidence Level B];

c. the presenting signs and symptoms of stroke [Evidence Level B];

d. the probability that the patient is acutely treatable with either intravenous alteplase and/or endovascular thrombectomy (EVT) [Evidence Level B];

e. patients are eligible for medical thrombolysis (intravenous alteplase) within 4.5-hours of known or presumed symptom onset [Evidence Level B];

f. some patients may be eligible for endovascular treatment when highly selected by neurovascular imaging up to 24-hour from known or presumed symptom onset. Transport time and receiving hospital projected treatment time must be considered when making transport and triage decisions [Evidence Level B];

g. the Emergency Department ability to provide acute stroke services within a target 90^{th} percentile for door-to-needle (i.e. arrival to treatment) time of 60 minutes (upper limit) and a target median door-to-needle time of 30 minutes or less [Evidence Level B],

h. other acute care needs of the patient [Evidence Level B].

iii. Patients with suspected stroke should be triaged by EMS personnel as Canadian Triage Acuity Scale (CTAS) Level 2 in most cases and as a CTAS Level 1 for patients with compromised airway, breathing or cardiovascular function [Evidence Level B].

a. For pediatric stroke cases, patients with suspected stroke should be triaged by EMS personnel as Pediatric Canadian Triage Acuity Scale (P-CTAS) Level 2 in most cases, and as a P-CTAS Level 1 for patients presenting with severe symptoms or compromised airway, breathing or cardiovascular function [Evidence Level C].

iv. **Pre-notification**: While enroute to the receiving hospital with acute stroke services, paramedics should notify the Emergency Department of the incoming suspected acute stroke patient, providing sufficient details such that a "Code Stroke" can be activated at that time [Evidence Level B].

a. Information required includes: time of stroke onset or time of symptom recognition or time when last known well (as accurate as possible), total symptom duration at

anticipated arrival in the Emergency Department, presenting signs and symptoms of stroke, Glasgow Coma Scale (GCS) score, CTAS triage score (or P-CTAS), patient age, current use of antithrombotic drugs, and expected time of arrival at the receiving hospital. *Refer to Section 3.4 and Box 3A for details of information required during pre-notification.*

v. Patients who are considered ineligible for thrombolytic therapy or endovascular thrombectomy should still be transported urgently (either directly or indirectly) to the closest hospital capable of providing services for the diagnosis and treatment of stroke (Emergency Department, access to neurovascular imaging, stroke unit, and stroke expertise on site or through Telestroke modalities) [Evidence Level C].

3.4 Hospital Arrival and EMS Handover to Emergency Department (ED) Staff

i. Transfer of care from paramedics to receiving hospital personnel should occur with minimal delay; patients with suspected hyperacute stroke who are potentially eligible for thrombolytic therapy or endovascular thrombectomy should receive the highest priority in the ED triage queue [Evidence Level B]. *Refer to Section 4.1 for more information.*

ii. Paramedics should provide the receiving hospital with the following information on hospital arrival: time of stroke onset or time of symptom recognition or time when last known well (as accurate as possible), total symptom duration at arrival in the ED, Glasgow Coma Scale score (GCS), CTAS triage score (or P-CTAS), patient age, comorbidities, current medications including antithrombotic drugs and medication allergies, and vital signs (including capillary glucose) [Evidence Level C].

a. Paramedics should ensure all information noted above is documented on the patient's emergency medical system record, and provided to the receiving hospital, during pre-notification and upon arrival to the hospital [Evidence Level B].

Clinical Considerations: *[New for 2018]*

1. Direct transport in many regions involves two considerations: (1) patients who may be eligible for intravenous alteplase may be directed to the closest centre (primary/advanced stroke centre or comprehensive stroke centre) and, (2) patients who are determined to be a likely candidate for endovascular thrombectomy may proceed directly to an EVT-enabled comprehensive stroke centre OR to the primary centre first to rapidly receive intravenous alteplase, and then be considered for transported to the EVT-enabled comprehensive stroke centre.
2. Screening for potential stroke and likelihood of large vessel occlusion should be done early in the on-scene assessment. If the stroke screen is positive, all actions on-scene from that point should be directed at moving to the ambulance and beginning transport. All treatments not immediately required (IVs, etc.) could be undertaken while the patient is enroute to the hospital or after hospital arrival. Scene time (location of patient at time of stroke) is an important variable that EMS professionals can control and needs to be monitored very closely. Time lost due to inefficient scene care cannot be made up during subsequent transport to hospital, regardless of the use of lights and sirens.
3. Pre-notification contact with the receiving Emergency Department should be as soon as possible; where possible, the paramedics and receiving Emergency Department physician or stroke team member should speak enroute.
4. The term 'eligible' for acute stroke therapies is usually defined within regional jurisdictions. Generally it refers acute stroke patients within the 4.5 hour time window for medical thrombolytic therapy, however local definitions should be clarified during implementation of these recommendations.

5. For endovascular thrombectomy, the strongest evidence for benefit exists for treatment received within 6 hours of stroke symptom onset (with or without concurrent medical thrombolytic therapy). However, randomized trial evidence exists to show that highly selected patients may be considered for endovascular thrombectomy based upon neurovascular imaging within a 24 hour window from symptom onset.
6. In some stroke centres, the alteplase treatment time window may extend beyond 4.5 hours under the directive of a research or local protocols. These factors should be taken into consideration during transport and agreements should be in place between the provincial/regional EMS system and the receiving hospitals.
7. In regions with a specialized pediatric hospital every attempt should be made to transport children with signs of stroke to that specialized pediatric hospital.

Box 3A: Core Information Required by Dispatch, Paramedics and Receiving Healthcare Facility

- Where permitted, name, date of birth, and / health card number of patient (Note, in general this confidential personal health information is not allowed to be transmitted by radio; however, some provinces have been able to receive a waiver and the restriction lifted for emergency cases such as stroke)
- *Location of patient*
- *Stroke Symptom onset time if witnessed, and last seen well time if not witnessed*
- *Presenting signs of stroke and stroke severity score, based on standardized screening tools*
- *Current condition of the patient having a stroke, including previous functional status/independence and changes in their condition since the stroke symptoms started*
- *Current medications if known (such as anticoagulants)*
- *Advanced care directives if any*
- *Additional health problems, if known*

Rationale

Hyperacute stroke is a medical emergency and optimizing out-of-hospital care improves patient outcomes. Emergency medical services play a critical role in out-of-hospital (prehospital) assessment and management of suspected stroke patients. Acute interventions such as thrombolytic therapy are time-sensitive and therefore strategies such as re-directing ambulances to stroke centres to facilitate earlier assessment, diagnosis, and treatment may result in better outcomes.

Newer endovascular thrombectomy treatments have with very strong, high-quality evidence that demonstrates patients with disabling ischemic stroke who meet imaging criteria have significant benefits from receiving these therapies. The strongest evidence supports endovascular thrombectomy within 6 hours from stroke symptom onset as a highly beneficial treatment in combination with intravenous thrombolysis (given within 4.5 hours of symptom onset), with numbers needed to treat reported as low as 3 – 4. Endovascular thrombectomy is also beneficial as a sole treatment among those ineligible for intravenous thrombolysis. In addition, a small group of patients may still benefit from endovascular thrombectomy up to 24 hours from symptom onset when selected by neurovascular imaging in the context of a coordinated stroke system, including experts in stroke and neurointerventional care.

System Implications

1. Programs to train all emergency medical services personnel regarding stroke recognition, assessment, management, and transport requirements in the pre-hospital phase of care.

2. Paramedic education that includes the recognition of the signs and symptoms of acute stroke, including knowledge of the FAST mnemonic, and the need to provide rapid and appropriate out-of-hospital assessment.
3. Ongoing paramedic education on the use of validated pre-hospital stroke screening protocols and tools and the ability to incorporate such protocols and tools into all pre-hospital assessments of suspected stroke patients. The Canadian Stroke Best Practice Recommendations include assessment tools and educational materials in collaboration with emergency medical service leaders for implementation across Canada.
4. Ambulance services in all parts of Canada with direct transport protocols and agreements (for bypass or redirect) between emergency medical service providers and regional health authorities and/or receiving hospitals.
5. Emergency medical services able to provide coordinated seamless transport (land, water, and air) and care for acute stroke patients.
6. Communication systems such as telemedicine to support access to specialized stroke services.
7. Protocols and agreements in place to support the transfer of patients with disabling stroke to hospitals that provide advanced acute stroke treatments including endovascular thrombectomy, regardless of geographic location.
8. Development of processes in each region that has both adult and pediatric acute services with criteria for transporting children with suspected stroke – based on symptoms and age – to pediatric versus adult stroke centres. These criteria should be agreed upon by both adult and pediatric centres, and EMS.
9. Development of processes for EMS that can help support evaluation of whether suspected stroke patients could be transported directly to comprehensive stroke centres that have endovascular thrombectomy services or undergo initial imaging and care at primary stroke centres.

Performance Measures

1. **Time from initial call received by emergency dispatch centre to patient arrival at an Emergency Department that provides stroke services.**
2. Percentage of (suspected) stroke patients arriving in the ED who were transported by EMS.
3. Proportion of acute stroke patients transported by EMS to a stroke enabled hospital (i.e. designated hyperacute stroke treatment centre) as first hospital destination. Target greater than or equal to 90%.
4. Proportion of acute stroke patients presenting to the ED as a result of EMS transport versus "walk in". Target greater or equal than 90%.
5. Time from initial call received by emergency dispatch centre to EMS arrival on scene.
6. Time from EMS arrival on scene to arrival at the receiving ED (ideally at a stroke centre providing acute stroke services).
7. Percent of EMS transports of ischemic stroke patients with symptoms less than 4.5 hours, and less than 6 hours, for which the receiving hospital received notification enroute (pre-notification) of an incoming acute stroke patient.
8. Percentage of EMS calls where out-of-hospital time is less than 3.5 hours from symptom onset time (or time last known well) to arrival at the ED (performance target is greater or equal to 75 percent).
9. Percentage of potential stroke patients transported by EMS who received a final diagnosis of stroke or transient ischemic attack in the ED or at hospital discharge.

10. For pediatric stroke patients, the time from initial presentation to any entry point in the healthcare system (such as primary care or pediatrician office, Emergency Department) with symptoms of stroke to a confirmed diagnosis of stroke is received.

Measurement Notes

a. Emergency department records and administrative databases track stroke patients who arrive by ambulance (land, air, or water) as a standard data element.
b. ”Appropriate” Emergency Department refers to an Emergency Department that has access to a CT scanner in the facility, provides access to acute thrombolysis, and has medical personnel with stroke expertise available for emergent consult.
c. Appropriate” Emergency Department may also refer to Emergency Departments in stroke centres that have access to endovascular thrombectomy.
d. An appropriate/acceptable ‘over-triage’ rate should be less than 15% - i.e., false positive stroke determinations. (Indicator 9).
e. Refer to the Canadian Stroke Performance Measurement Manual for additional measures related to hospital bypass and pre-notification. (new link)

Implementation Resources and Knowledge Transfer Tools

Health Care Provider Information

- Canadian Triage Acuity Scale for adults (CTAS) and Pediatric Scale (P-CTAS): http://caep.ca/resources/ctas#intro
- Canadian Stroke Best Practice Recommendations Module: Appendix Two Tables 2A Standardized Acute Stroke Out-of-Hospital Diagnostic Screening Tools, and 2B Pre-Hospital Stroke Severity Scales
- FAST Signs of Stroke: www.heartandstroke.ca/fast

Patient Information

- FAST Signs of Stroke: http://www.heartandstroke.ca/fast
- “Your Stroke Journey”: http://www.strokebestpractices.ca/wp-content/uploads/2015/03/YOURSTROKEJOURNEY.FINAL_.ENGLISH..pdf\
- Post-stroke Checklist: http://www.strokebestpractices.ca/wp-content/uploads/2017/10/CSBP_Post_Stroke_Checklist_EN.pdf

Summary of the Evidence 2018f

Patients arriving to hospital using EMS (emergency medical services) following a stroke experience fewer delays in receiving appropriate diagnostic tests (e.g. brain imaging) and are more likely to receive t-PA, if eligible. Patients are also more likely to receive timely transportation and care when pre-notification systems, including the use of trained EMS dispatchers, are adopted. Watkins et al. (2013) reported that the percentage of patients whose final diagnosis was stroke increased significantly (63% to 80%, $p<0.01$) after EMS dispatchers completed training, aimed at improving their ability to detect suspected stroke patients. In a study that included 27,566 patients who were identified as suspected stroke patients by dispatchers, the mean times associated with transportation, including time to scene, time at scene, time from scene to destination and total transportation time were all significantly reduced, compared to persons whose final diagnosis was stroke, but who were not identified by dispatchers (Caceres et al. 2013). Berglund et al. (2012) reported that patients in the Hyper Acute STroke Alarm (HASTA) Study

assigned an upgraded priority level by dispatching personnel experienced fewer delays along the chain of stroke care from symptom onset to arrival at a stroke unit and were more likely to be treated with t-PA compared with patients who had been assigned to a standard-priority level by the emergency medical communications centre. Patients classified as Priority Level 1 received thrombolysis more often than those classified as priority level 2 (24% vs. 10%, p<0.001) and a greater number arrived at the stroke unit within 3 hours of symptom onset (61% vs. 46%, p=0.008).

Hospital pre-notification typically involves informing emergency department physicians and other relevant personnel (blood and EKG technicians, radiologists and pharmacologists) of the arrival of a potential stroke patient. The results from several studies indicate that the process indicator associated with thrombolysis treatment may be shortened for patients arriving to hospitals by EMS with prenotification protocols. Lin et al. (2012) included data from 371,988 acute ischemic stroke patients from the Get with the Guidelines database and reported that among patients transported to hospital using EMS pre-notification, they had significantly shorter door-to-imaging time (26 vs 31 mins, p<0.001), door-to-needle time (78 vs 81 mins, p<0.001), and stroke onset-to-needle time (141 vs 145 mins, p<0.001). Furthermore, of those who arrived at hospital within 2 hours of stroke onset, patients with a pre-notification were significantly more likely than those without to receive t-PA within 3 hours of stroke onset (73% vs 64%, p<0.001). In another US study based on registry data (Patel et al. 2011), of 13,894 patients who whose discharge diagnosis was stroke, patients arriving by EMS with hospital pre-notification were more likely to have brain imaging completed within 25 min (RR= 3.0, 95% CI 2.1-4.1) and to have the results interpreted within 45 min (RR= 2.7, 95% CI 2.3-3.3) compared to arriving by private transport. Patients eligible for t-PA were more likely to receive it if arriving by EMS with pre-notification (RR=1.5, 95% CI 1.1-1.9). Dalloz et al. (2012) included the results from 10 studies in a systematic review examining the use of pre-hospital stroke codes. A stroke code system was defined as efforts to improve the identification, transport and presentation of suspected stroke patients to the emergency department. The odds of treatment with thrombolysis were highest in settings that had a pre-hospital stroke code system in place compared with facilities with no stroke code (OR= 5.43, 95% CI: 3.84-7.73, p<0.001), and were lower in studies comparing pre-hospital stroke code with in-hospital stroke codes (OR=1.97, 95% CI: 1.53-2.54, p<0.001).

In the last several years, as endovascular techniques are becoming more widely available, several on-scene screening tools to identify patients with large vessel occlusions (LVO), designed for use by EMS technicians, have emerged. Examples of these scales include Field Assessment Stroke Triage for Emergency Destination (FAST-ED) (Lima et al. 2016), Vision, Aphasia, and Neglect (VAN) (Taleb et al. 2016), the Prehospital Acute Stroke Severity Scale (PASS) (Hastrup et al. 2016), Cincinnati Prehospital Stroke Severity Scale (CPSSS) (Katz et al. 2015), and The Los Angeles Motor Scale (LAMS) (Nazliel et al. 2008). Most of these scales are based on 3-6 selected items from the National Institutes of Health Stroke Scale. The sensitivities and specificities associated with these scales range from 61% to 100% and 40% to 92%, respectively. Smith et al. (2018) included the results from 36 studies evaluating the accuracy of LVO prediction scales in patients with suspected stroke or presumed acute ischemic stroke in pre-hospital or emergency department settings. The authors concluded that no scale had both high sensitivity and specificity to determine the presence vs. absence of LVO, and that in clinical practice that the probability of LVO given a negative test could still be ≥10%.

The use of mobile stroke units, ambulances which are equipped with specialized equipment, such as on-site laboratories and CT scanners, and are staffed with additional personnel with stroke expertise, are now appearing in some large, urban cities. Their feasible and effectiveness are the subjects of ongoing investigation. Kunz et al. (2016) compared the outcomes of patients who received thrombolysis therapy

using the mobile stroke unit, STEMO from 2011-2015 with patients who received thrombolysis, but arrived at hospital via traditional emergency medical services. A significantly higher proportion of patients in the STEMO group were treated ≤ 90 minutes of stroke (62% vs. 35%, p<0.0005) and were living without severe disability at 3 months (83% vs. 74%, p=0.004). The 3-month mortality was also significantly lower in the STEMO group (6% vs. 10%, p=0.022). However, there was no significant difference in the primary outcome, the number of patients who achieved an excellent outcome (mRS 0-1) at 3 months (53% STEMO vs. 47% conventional, p=0.14). There were no significant differences in the safety outcomes between the 2 groups (sICH 3% vs. 5%, p=0.27 and 7-day mortality 2% vs. 4%, p=0.23). Adjusting for baseline characteristics, STEMO was an independent predictor of living without severe disability at 3 months (OR=1.86, 95% CI 1.20-2.88, p=0.006), but not for the primary outcome (OR=1.40, 95% CI 1.00-1.97, p=0.052). In an earlier study examining the use of STEMO, (Ebinger et al. 2014), among patients for whom STEMO was deployed, the mean alarm-to-treatment time for patients who received thrombolysis was reduced by 25 minutes, compared with control weeks. Of the eligible patients, t-PA was used in 32.6% of STEMO deployment cases, 29% during STEMO weeks, and 21.1% during control weeks.

Reference List and Evidence Tables

Evidence Table 2 and References available on website at www.strokebestpractices.ca

Section Four: Emergency Department Evaluation and Management of Patients with TIA and Acute Stroke (Sixth Edition, 2018)

4. Emergency Department Evaluation and Management of Patients with TIA and Acute Stroke Recommendations

4.0 Emergency Department Evaluation

i. All patients presenting to an Emergency Department with suspected acute stroke or transient ischemic attack must have an immediate clinical evaluation and investigations to establish a diagnosis, rule out stroke mimics, determine eligibility for intravenous thrombolytic therapy and endovascular thrombectomy treatment (EVT), and develop a plan for further management, including goals for care [Evidence Level A].

Note: If initial brain imaging reveals a hemorrhagic stroke, then refer to new CSBPR for Hemorrhagic Stroke for guidance on further investigations, acute treatments and ongoing management. (For release Fall 2018)

4.1 Initial ED Evaluation

i. Patients with suspected acute stroke should have a rapid initial evaluation for airway, breathing and circulation [Evidence Level A].

ii. A neurological examination should be conducted to determine focal neurological deficits and assess stroke severity [Evidence Level A].

   a. A standardized stroke scale should be used (such as the National Institutes of Health Stroke Scale [NIHSS) [Evidence Level C].

iii. Assessment in the acute phase should include heart rate and rhythm, blood pressure, temperature, oxygen saturation, hydration status, and presence of seizure activity [Evidence Level B].

iv. Acute blood work should be conducted as part of the initial evaluation [Evidence Level B]. Initial blood work should include: electrolytes, random glucose, complete blood count (CBC), coagulation status (INR, aPTT), and creatinine. *Refer to Table 2B for Recommended Laboratory Investigations for Acute Stroke and Transient Ischemic Attack for additional information.*

   a. ***Note, these tests should not delay imaging or treatment decisions and treatment initiation*** for intravenous thrombolysis and endovascular thrombectomy.

v. **Seizure Assessment:** New-onset seizures at the time of an acute stroke, occurring either immediately before or within 24 hours of the stroke onset, should be treated using appropriate short-acting medications (e.g. lorazepam IV) if they are not self-limited [Evidence Level C].

   a. A single, self-limiting seizure occurring at the onset, or within 24 hours after an acute stroke (considered an “immediate” post-stroke seizure) should not be treated with long-term anticonvulsant medications [Evidence Level C].

   b. Patients that have an immediate post-stroke seizure should be monitored for recurrent seizure activity during routine monitoring of vital signs and neurological status. Recurrent seizures in patients with ischemic stroke should be treated as per treatment recommendations for seizures in other neurological conditions [Evidence Level C].

   c. Seizures are a common presentation with stroke in neonates and children. Consider enhanced or prolonged electroencephalogram (EEG) in at-risk populations such as neonates, children with stroke and adults with otherwise unexplained reduced level of

consciousness [Evidence Level C].

d. Prophylactic use of anticonvulsant medications in patients with acute stroke is not recommended [Evidence Level C]. There is no evidence to support the prophylactic use of anticonvulsant medications in patients with acute stroke and there is some evidence to suggest possible harm with negative effects on neural recovery.

4.2 Neurovascular (Brain and Vascular) Imaging (For 2018, all imaging recommendations have been consolidated into this section)

i. All patients with suspected acute stroke should undergo brain imaging with non-contrast CT or MRI [Evidence Level A].

ii. All patients with suspected acute ischemic stroke who arrive **within 4.5 hours** and are potentially eligible for intravenous thrombolysis (*Refer to criteria in Box 4A, 5B*) should undergo ***immediate*** brain imaging with **non-contrast CT (NCCT)** without delay to **determine eligibility for thrombolysis** [Evidence Level A].

iii. All patients with suspected acute ischemic stroke who arrive **within 6 hours** and are potentially eligible for endovascular thrombectomy *(refer to criteria in Box 4B, 5C*) should undergo ***immediate*** brain imaging with **non-contrast CT and CT angiography (CTA)** without delay, from arch-to-vertex including the extra- and intra-cranial circulation, to identify large vessel occlusions **eligible for endovascular thrombectomy** [Evidence Level A].

Note: Primary stroke centres that cannot do CTA should have pre-planned arrangements for rapid transfer of appropriate patients. They should complete NCCT and offer intravenous alteplase as appropriate and then rapidly transfer the patient to a CSC for more advanced imaging and consideration for EVT.

a. A validated triage tool (such as ASPECTS) should be used to rapidly identify patients who may be eligible for endovascular thrombectomy treatment and may require transfer to a different facility for EVT [Evidence Level B]. [New for 2018]

b. Advanced CT imaging such as CT perfusion (CTP) or multiphase or dynamic CTA (to assess pial collateral vessels) can be considered as part of initial imaging to aid patient selection [Evidence Level B]. However this must not substantially delay decision and treatment with intravenous thrombolysis with alteplase or endovascular thrombectomy treatment. *Refer to Box 4C and 5C.*

Note: if there are signs of hemorrhage on initial CT images there is no need to proceed to CTP imaging as part of initial imaging and CTA should be completed based on the clinical judgement of the treating physician.

iv. All patients with suspected ischemic stroke who arrive at **6-24 hours** after stroke onset (late presentation and stroke on awakening with unknown onset time) and are potentially eligible for late window endovascular thrombectomy treatment *(Refer to Box 4D)* should undergo ***immediate*** brain imaging with non-contrast CT with CTA and CT perfusion, or MRI with MRA and MRP [Evidence Level B]. *Note: In most Canadian centres a CT approach may be more practical and more readily available than an MR approach. Choice of imaging modality should be based on most immediate availability and local resources.*

Refer to Section 5 for information on alteplase administration and endovascular thrombectomy.

4.3 Acute Blood Pressure Management

i. The ideal level of blood pressure target to achieve and sustain in the hyperacute phase is unknown at this time. Pharmacological agents and routes of administration should be chosen to avoid precipitous falls in blood pressure [Evidence Level C].

ii. **Ischemic stroke patients eligible for thrombolytic therapy**: Very high blood pressure (greater

than 185/110 mm Hg) should be treated concurrently with thrombolysis to reduce the risk of hemorrhagic transformation [Evidence Level B]. Blood pressure should be lowered and sustained below 185/110 prior to alteplase therapy and to below 180/105 mmHg for the next 24 hours after alteplase administration [Evidence Level C].

iii. **Ischemic stroke patients not eligible for thrombolytic therapy**: Treatment of hypertension in the setting of acute ischemic stroke or transient ischemic attack should not be routinely treated [Evidence Level C].

iv. Extreme blood pressure elevation (e.g. systolic BP greater than 220 or diastolic BP greater than 120 mmHg) should be treated to reduce the blood pressure by approximately 15 percent, and not more than 25 percent, over the first 24 hours with further gradual reduction thereafter to targets for long-term secondary stroke prevention [Evidence Level C].

v. Avoid rapid or excessive lowering of blood pressure because this might exacerbate existing ischemia or might induce ischemia, particularly in the setting of intracranial or extracranial arterial occlusion [Evidence Level C].

vi. Choice of agents for managing blood pressure should be based on current Hypertension Canada Blood Pressure treatment guidelines (www.hypertension.ca)

Note: For guidance on blood pressure management of hemorrhagic stroke, refer to Canadian Stroke Best Practices Management Intracerebral Hemorrhagic Stroke module (new recommendations, expected release Fall 2018)

4.4 Cardiovascular Investigations

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

ii. Unless a patient is hemodynamically unstable, electrocardiogram should not delay assessment for intravenous thrombolysis and endovascular thrombectomy and can be deferred until after a decision regarding acute treatment is made [Evidence Level C].

Note: For patients being investigated for an acute embolic ischemic stroke or TIA of undetermined source whose initial short-term ECG monitoring does not reveal atrial fibrillation but a cardioembolic mechanism is suspected, refer to Canadian Stroke Best Practices Secondary Prevention of Stroke module, section 7 on Management of Atrial Fibrillation in Stroke for additional information.

iii. Echocardiography (2D or TEE) may be considered in patients where a cardiac cause of stroke is suspected, including in young adults and children who present with stroke, and when infectious endocarditis is suspected [Evidence Level C].

4.5 Blood Glucose Abnormalities

i. All patients with suspected acute stroke should have their blood glucose concentration checked upon arrival to the Emergency Department (*note: For patients arriving by EMS, the capillary glucose measured by EMS should be reviewed by the Emergency Department team for any immediate management required)* [Evidence Level B]. *Refer to Table 2B Recommended Laboratory Investigations for Patients with Acute Stroke or Transient Ischemic Attack for further details. Refer Section 3 of this module for further details regarding EMS management.*

ii. Hypoglycemia should be corrected immediately [Evidence Level B].

iii. Although no optimal glucose target has been identified, it is reasonable to treat hyperglycemia which has been associated with hemorrhagic transformation when treating with IV alteplase thrombolysis [Evidence Level C].

4.6 Additional Management Considerations in the Emergency Department

i. **Chest X-Ray:** A chest x-ray should be completed when the patient has evidence of acute heart disease or pulmonary disease [Evidence Level B]. Unless a patient is hemodynamically unstable, chest x-ray can be deferred until after a decision regarding acute treatment and it should not delay assessment for thrombolysis and endovascular thrombectomy.

ii. **Swallowing Assessment**: Patient swallowing screen should be completed as early as possible by a practitioner trained to use a validated swallowing screening tool as part of initial assessment, **but should not delay decision-making regarding eligibility for acute stroke treatments [**Evidence Level A].

   a. Ideally swallow screening should be done within 24 hours of hospital arrival, including patients that receive acute stroke treatments (intravenous alteplase and endovascular thrombectomy) [Evidence Level C].

   b. Patients should remain NPO (nil per os - no oral intake) until swallowing screen completed for patient safety [Evidence Level B];

   c. Oral medications should not be administered until swallowing screen using a validated tool has been completed and found normal [Evidence Level B]; alternate routes such as intravenous and rectal administration should be considered while a patient is NPO;

   d. A patient's clinical status can change in the first hours following a stroke or TIA, therefore patients should be closely monitored for changes in swallowing ability following initial screening [Evidence level C];

   e. Patients found to have abnormal swallowing ability on screening should be referred to a healthcare professional with expertise in swallowing assessments for an in-depth swallowing assessment [Evidence Level B].

   Refer to Section 9, and Stroke Rehabilitation Module, Section 7, for additional information on screening for swallowing ability and dysphagia management.

iii. **Urethral Catheters:** The use of chronic indwelling urethral catheters should generally be avoided due to the risk of urinary tract infections [Evidence Level A]. *Refer to Section 9 for additional information.*

   a. Insertion of an indwelling urethral catheter could be considered for patients undergoing endovascular thrombectomy, but should not delay achieving reperfusion. The need for retaining the catheter should be reconsidered after the end of the endovascular thrombectomy procedure, and it should be discontinued as soon as the patient can be expected to resume voiding on their own [Evidence Level C].

   b. Insertion of an indwelling urethral catheter is not routinely needed prior to intravenous thrombolysis, unless the patient is acutely retaining urine and is unable to void. If inserted for patient-specific reasons, it should not delay acute treatment [Evidence Level C].

   c. If used, indwelling catheters should be assessed daily and removed as soon as possible [Evidence Level A].

   d. Fluid status and urinary retention should be assessed as part of vital sign assessments [Evidence Level C].

   e. Excellent pericare and infection prevention strategies should be implemented to minimize risk of infections [Evidence Level C].

iv. **Temperature** should be routinely monitored and treated if above 37.5 Celsius [Evidence Level B]. *Refer to Canadian Stroke Best Practice Recommendations Acute Inpatient Stroke Care Module, Section 2.3, for additional information.*

v. **Oxygen:** Supplemental oxygen is not required for patients with normal oxygen saturation levels [Evidence Level C].

Clinical Considerations: (New for 2018)

i. There is no evidence to support the practice of routine reversal of anticoagulation, either during non-thrombolytic conservative care or in order to give alteplase in patients presenting with acute ischemic stroke who are on warfarin or direct oral anticoagulants. Endovascular thrombectomy may be considered despite anticoagulation if patients are otherwise eligible.

Box 4a: Alteplase Selection Imaging Exclusion Criteria: CT Findings

1. CT showing early signs of extensive infarction.
2. Signs of hemorrhagic stroke on CT imaging.

Refer to Section 5 for additional intravenous alteplase clinical inclusion and exclusion criteria.

Box 4B: Endovascular Selection Imaging Criteria for Patients Arriving within 6 Hours of Stroke Onset

1. A small-to-moderate ischemic core (which may be estimated as an ASPECT score of 6 or higher).
   - For patients with a large ischemic core, such as with an ASPECT score less than 6, the decision to treat should be based on the potential benefits and risks of the treatment, made by a physician with stroke expertise in consultation with the neuro-interventionalist, and patient and/or family/substitute decision-makers.
2. Intracranial artery occlusion in the anterior circulation, including proximal large vessel occlusions in the distal ICA or MCA and immediate branches.
3. For patients with basilar artery occlusions, the decision to treat with endovascular thrombectomy should be based on the potential benefits and risks of the therapy, made by a physician with stroke expertise in consultation with the neuro-interventionist, and the patient and/or decision-makers. *Note: there are ongoing randomized trials in this area and this issue will be reviewed once the results become available.*

Refer to Section 5 for additional endovascular thrombectomy clinical inclusion and exclusion criteria.

Box 4C: Advanced CT Imaging Criteria for Endovascular Thrombectomy Selection

1. Sites using CT perfusion imaging should utilize software that provides reproducible objective measurements of ischemic core and penumbra.
2. An occluded proximal intracranial artery (carotid artery, M1 segment of the MCA, or proximal M2 divisions) of the anterior circulation, which is a target lesion amenable to endovascular thrombectomy. The location of occlusion is defined by an arterial phase CTA from ascending aorta to the vertex of the head. Inclusion of the aortic structures allows planning and assessment of the technical feasibility of an endovascular approach to the occluded intracranial artery.
3. There is evidence to suggest that moderate-to-good pial collateral filling (as defined by CTA), or evidence of CT perfusion mismatch predict a better response to endovascular thrombectomy.
4. Stroke imaging on-site with 24-hour access, seven days a week, including a computed tomography (CT) scanner (i.e. 3rd generation or higher helical scanner) with programming for CT angiography (CTA); multiphase or dynamic CTA or CT perfusion (CTP) imaging can also be used if available on-site.

Note: ASPECTS score is one tool to estimate core: A small-to-moderate ischemic core can be defined by an ASPECTS score of 6 or higher on non-contrast computed tomography (NCCT) or areas of low cerebral blood volume (CBV) or cerebral blood flow (CBF) maps on CT perfusion imaging.

Box 4D: Endovascular Selection Imaging Criteria for Patients Arriving Later than 6 Hours of Stroke Onset

1. Sites using CT perfusion imaging should utilize software that provides reproducible objective measurements of ischemic core and penumbra.
2. An occluded proximal intracranial artery (carotid artery, M1 segment of the MCA, or proximal M2 divisions) of the anterior circulation, which is a target lesion amenable to endovascular thrombectomy. The location of occlusion is defined by an arterial phase CTA from ascending aorta to the vertex of the head. Inclusion of the aortic structures allows planning and assessment of the technical feasibility of an endovascular approach to the occluded intracranial artery.
3. Imaging and clinical evidence of small core and large area at risk, defined in the trials as either:
    a. NIHSS ≥10 and either 0-21 ml core infarct (≥80 years old) or 0-31 ml core infarct (<80 years old), or NIHSS ≥20 and 31 to <51 ml core infarct and <80 years old (DAWN trial criteria).

    OR

    b. Ischemic core volume is < 70 ml, mismatch ratio is >/= 1.8 and mismatch volume* is >/= 15 ml (DEFUSE3 trial criteria).

Adapted from: **DAWN Imaging Criteria (up to 24 hours):** (Nogueira RG et al; N Engl J Med. 2018 Jan 4;378(1):11-21); **DEFUSE3 Imaging Criteria (up to 16 hours):** **h**ttps://clinicaltrials.gov/ct2/show/NCT02586415

Rationale

Patients who present to hospital with suspected stroke often also have significant physiological abnormalities and comorbidities. These can complicate management of stroke. Signs and symptoms that may explain the cause of the stroke or predict later complications (such as space-occupying infarction, bleeding, or recurrent stroke) and medical conditions such as hypertension or the presence of a coagulopathy, will have an impact on treatment decisions. An efficient and focused assessment is required to understand the needs of each patient.

It is impossible to reliably differentiate infarct from hemorrhage by clinical examination alone. Brain imaging is required to guide management, including the selection of time-sensitive acute stroke treatments. A CT scan or magnetic resonance (MR) imaging is essential to differentiate between ischemic stroke and intracerebral hemorrhage, and stroke mimics, since clinicians may disagree on the clinical diagnosis of stroke (versus not stroke) in about 20 percent of patients.

Initial management of elevated blood pressure in acute stroke patients remains controversial due to the lack of evidence to clearly guide practice. At the same time, this is an area where clinicians often seek guidance from stroke specialists. The recommendations for this area emphasize caution and diligence in monitoring and treating extremely high blood pressure in the first hours after stroke onset.

Diabetes is a major modifiable risk factor for vascular disease that may be first diagnosed at the time of a stroke at the time acute stroke is associated with increased size of the infarcted area in experimental animals, a greater risk of symptomatic hemorrhage after intravenous alteplase treatment, and is associated with poor clinical outcomes in epidemiological studies.

System Implications

1. Local protocols to ensure all stroke patients have rapid access to computed tomography (CT) with CT angiography (CTA) of the extracranial and intracranial vessels completed at the same time as the initial brain imaging.
2. Protocols for ‘code stroke’ activation of the stroke team and diagnostic services prompted by receiving pre-notification by paramedics of an incoming suspected stroke patient.
3. Protocols should be in place to prioritize suspected stroke patients in triage queues at emergency departments to ensure timely access to diagnostic services and EVT, where applicable.
4. Agreements to ensure patients initially managed in rural hospitals without neurovascular imaging capability have timely access to CTA with imaging of the extracranial and intracranial vessels at partnering hospitals.
5. Protocols and standing orders to guide initial blood work and other clinical investigations.
6. Local protocols, especially in rural and remote locations, for rapid access to clinicians experienced in interpretation of diagnostic imaging, including access through telemedicine technology.
7. Provinces and regions should ensure availability of physicians and other healthcare professionals with stroke expertise, including recruitment and retention strategies to increase accessibility of acute stroke services for all Canadians.

Performance Measures

1. Median time from patient arrival to hospital to first/qualifying imaging scan.

2. Median time from patient arrival to hospital to first CTA of extracranial and intracranial vessels.
3. Proportion of stroke patients who receive initial brain imaging (either CT or CTA) within 30 minutes of hospital arrival for those patients who arrive within acute stroke treatment times.
4. Proportion of stroke patients who receive a brain CT/CTA within 24 hours of hospital arrival (core).
5. The proportion of patients with carotid territory events who undergo carotid imaging in the ED.
6. The proportion of patients who do not have carotid imaging in the ED but who have arrangements made for carotid imaging as an outpatient.
7. The median time from CBC, INR and thrombin time, Cr/eGFR draw to having results available.
8. Proportion of patients with blood glucose levels documented during assessment in the Emergency Department.
9. Proportion of stroke patients who receive a CT scan in less than 25 minutes from hospital arrival in patients arriving less than 4.5 hours from last known well time, and without contraindications to thrombolysis.
10. Median time from stroke symptom onset to carotid imaging.

Measurement Notes

a. Data may be obtained from laboratory reports or patient chart.
b. CT and CTA imaging time should be based on time of first slice by the scanner. Specify in your results which type of scan (CT or CTA, separately or combined) was being measured and reported
c. Stratify analysis for patients who arrive within 3.5 hours of stroke symptom onset and those who arrive within 4.5, 6 and 24 hours from stroke symptom onset.
d. Performance measure 1: apply to patients who may be candidates for acute thrombolysis (i.e. who arrive at hospital within 4.5 hours of stroke onset) and for patients who may be eligible for other time-sensitive interventions.
e. Performance measures 1 and 2: Time interval measurements for CT and MRI should be calculated from the time the patient enters the Emergency Department until the time noted on the actual brain imaging scan.
f. Performance measure 3: For outpatient carotid imaging, a notation should appear in the discharge summary, or in nursing notes, with an indication that the test has actually been requested or requisitioned prior to the patient leaving the hospital.
g. Performance measure 5: Use medical history to determine whether patient was known to have diabetes prior to the stroke event.

Implementation Resources and Knowledge Transfer Tools

Health Care Provider Information

- Canadian Stroke Best Practices Appendix Two, Table 2A: Screening and Assessment Tools for Acute Stroke Severity
- Canadian Stroke Best Practices Acute Stroke Management Section 2, Table 2B: Recommended Laboratory Investigations for Acute Stroke and Transient Ischemic Attack
- HSF Stroke Assessment Pocket Cards: http://www.strokebestpractices.ca/wp-content/uploads/2017/07/002-17_CSBP_StrokeAssessPocketGuide_7.5x4.25_EN_v6_LR.pdf

- Canadian Cardiovascular Society Atrial Fibrillation Guidelines 2016: http://www.onlinecjc.ca/article/S0828-282X(16)30829-7/fulltext
- American College of Chest Physicians (ACCP) Guidelines for Diagnosis & Management of DVT / PE, 9th Ed.: http://professionalsblog.clotconnect.org/2012/02/27/new-accp-guidelines-%E2%80%93-dvt-and-pe-highlights-and-summary/
- Canadian Association of Radiologists 2012 guidelines: http://www.car.ca/en/standards-guidelines.aspx
- Hypertension Canada treatment guidelines www.hypertension.ca

Patient Information

- Signs of stroke: FAST Signs of Stroke
- Stroke information: http://www.heartandstroke.ca/stroke/what-is-stroke
- Atrial Fibrillation information: www.heartandstroke.ca/bepulseaware
- Patient Atrial Fibrillation modules: http://www.heartandstroke.ca/heart/conditions/atrial-fibrillation

Summary of the Evidence 2018

Initial Assessment

Patients require immediate evaluation when presenting to the Emergency Department (ED) with suspected stroke or transient ischemic attack (TIA). For those patients presenting with TIA, their risk for imminent stroke (i.e. within one week) can be evaluated, and investigations/treatment initiated to prevent a future stroke. Standard assessments for patients with suspected acute stroke include a neurological examination, monitoring of vital signs, blood work, imaging and cardiovascular investigations, dysphagia screens and seizure assessment. It is also important to identify patients who are TIA 'mimics', to avoid unnecessary and expensive investigations, incorrect diagnostic labelling and inappropriate long-term prevention treatments. Patients presenting with stroke symptoms may ultimately be diagnosed with other conditions such as migraine headache, vertigo, metabolic disturbances, brain tumors, presyncope/ syncope or anxiety (Karliński et al. 2015, Lee & Frayne 2015). The percentage of stroke mimics among patients presenting to the emergency department with acute symptoms has been estimated to be approximately 30% (Goyal et al. 2016, Merino et al. 2013).

Neurovascular Imaging

Immediate access to brain and vascular imaging is required for all patients arriving to hospital with suspected stroke or TIA. A non-contrast CT scan is considered the imaging standard to be used initially to identify acute ischemic stroke and to rule out intracranial hemorrhage. CT scans are quick to perform, easy to tolerate, and are known to be very reliable for the detection of intracerebral hemorrhage. Early detection of hemorrhage is essential since the presence of blood in the brain or subarachnoid space is the main contraindication for the administration of aspirin, anticoagulants and thrombolytic therapy. Early imaging is particularly important for patients who may be potential candidates for thrombolytic therapy, since it has a narrow therapeutic window for administration. Wardlaw et al. (2004) found that a computed tomography (CT) scan for all patients with suspected stroke on admission to hospital was the most cost-effective strategy, despite the increased cost of scans being performed during "off hours". The higher costs were offset by savings realized through decreased lengths of hospital stay.

CT angiography (CTA) should be performed as part of the initial acute stroke CT imaging protocol. It is fast, simple and helps to identify patients with small core infarcts (ASPECTS 6 or higher) in the anterior circulation, who should be considered for endovascular therapy. Either multiphase or dynamic CTA is recommended over single-phase CTA, as the former can be used to assess for both intracranial arterial occlusion and also pial arterial collateral circulation (Menon et al. 2015). Evidence of adequate pial collaterals may predict better response to reperfusion and outcomes in acute ischemic stroke patients (Christoforidis et al. 2005). CTA is well-tolerated with a very low risk of allergic reaction or renal impairment from contrast administration, and does not pharmacologically interact with t-PA.

CT perfusion (CTP) is another advanced CT imaging modality that can be used to determine infarct core size (based on cerebral blood volume [CBV] maps) and ischemic penumbra (using cerebral blood flow [CBF] or time maps). CTP has been used in recent trials of endovascular therapy to identify patients who were candidates for treatment. In the EXTEND-IA trial, (Campbell et al. 2015), inclusion required a 20% mismatch between core infarct and ischemic penumbra identified using CTP. Due to variability in vendor software, specific CBV volume cut-offs for core infarct size is not standardized. The use of CTP for acute stroke patients should be reserved for centres with well-established CTP protocols and experience in interpreting CTP, or the use of quantitative CTP software, and must not substantially delay decisions for acute stroke treatments.

While CT scans are recommended for initial brain imaging following stroke, there are cases where magnetic resonance imaging (MRI) with diffusion-weighted sequences (DWI) may be superior. MRI has been shown to be more sensitive in detection of the early changes associated with ischemia, especially in patients with small infarcts. Using the results from 8 studies, Brazzelli et al. (2009) reported that the sensitivity of magnetic resonance imaging (MRI) may be higher than CT scans for the identification of ischemic stroke (99% vs. 39%), although the authors questioned the generalizability of their findings. If an MRI is available and performed in place of CT, enhanced imaging in the form of DWI, GRE and FLAIR is indicated. Brunser et al. (2013) included 842 patients admitted to the Emergency Department with a suspected ischemic stroke. Diffusion-weighted imaging (DWI) examinations were performed for all patients. For patients with a final diagnosis of stroke, the sensitivity of DWI in detecting ischemic stroke was 90% (95% CI 87.9 to 92.6), and specificity was 97% (95% CI 91.8 to 99.0).

Cardiovascular Investigations

An electrocardiogram (ECG) should be performed immediately to identify arrhythmias for all patients with stroke and TIA presenting to the Emergency Department. Atrial fibrillation (AF) is commonly diagnosed post-stroke, and is of particular concern due to its role in forming emboli. Sposato et al. (2015) included the results from 11 studies in which cardiac monitoring was initiated in the ED. An estimated 7.7% of patients, without a history of AF, were newly diagnosed. Suissa et al. (2012) included 946 patients with ischemic stroke without history of AF and found that the odds of detection were greatest within the first 24 hours of stroke (OR= 9.82; 95% CI 3.01 to 32.07). Patients who received continuous cardiac monitoring group were more likely to be identified with AF compared with those who received a baseline ECG, 24-hour Holter monitor and additional ECGs when necessary (adj OR= 5.29; 95% CI 2.43 to 11.55). Regardless of the type of monitoring used, the initial ECG will not always detect all cases of AF. In the same study, it was found that ECG monitoring beyond the baseline assessment resulted in the identification of additional cases of AF in 2.3%-14.9% of the population (Suissa et al. 2012). The use of serial ECG assessments over the first 72 hours following stroke can be an effective means of diagnosing AF. For example, Douen et al.(2008) reported there was no significant difference in detection rates between cardiac monitoring groups. AF was identified in 15 new patients using serial ECG and in 9 new patients using a Holter monitor. The majority of these cases were identified within 72

hours (83%).

The use of a transesophageal echocardiography (TEE) is indicated when there is suspected cardiac embolism involvement. For patients with an unknown cause of stroke following baseline diagnostic assessments, and no contraindications to anticoagulation therapy, TEE was found to identify possible sources of cardiac embolism (de Bruijn et al. 2006). In 231 patients with recent stroke (all types) or TIA, TEE was found to perform significantly better than transthoracic echocardiography (TTE) in identifying possible sources of cardiac embolism (55% vs. 39%). Among the 39 patients ≤45 years, a potential cardiac source was identified in 13 patients. Of these, the abnormality was identified by TEE in 10 cases and in 3 cases using TTE. Among 192 patients >45 years, a potential cardiac source of embolism was identified in 59% of patients. TEE confirmed the potential cardiac source in 34 patients, but also detected a potential cardioembolic source in an additional 80 patients.

Acute Blood Pressure Management

There is no evidence to suggest that interventions to manage extreme perturbations in blood pressures with vasoactive agents help to improve stroke outcome. In the CATIS trial (He et al. 2014), 4071 patients with acute ischemic stroke were randomized to receive or not receive antihypertensive therapy during hospitalization. Although mean systolic blood pressure was significantly lower among patients in the intervention group, treatment was not associated with significant reduction in the risk of death or major disability at either 14-days (OR= 1.00, 95% CI 0.88 to 1.14) or 3-months (OR= 0.99, 95% CI 0.86 to 1.15) following study entry. Two Cochrane reviews have examined the potential benefits of artificially raising and lowering blood pressure with vasoactive drugs within the first week of stroke. One of the reviews was restricted to the inclusion of RCTs, and included the results from 12 trials (Geeganage & Bath, 2008), while the other included non RCTs as well (Geeganage & Bath, 2010). In both reviews, the focus of most of the included studies was blood pressure reduction. Treatment was associated with significant early and late reductions in SBP and DBP, but was not associated with significant reduction in the risk of death or a poor outcome within one month, or the end of follow-up. However, the use of vasoactive drugs used to raise blood pressure significantly increased in the odds of death or disability at the end of the trial (OR= 5.41; 95% CI 1.87 to 15.64) (Geeganage & Bath, 2010). Further evidence from a meta-regression study (Geeganage & Bath, 2009), which included the results from 37 trials, also suggests that large changes in blood pressure in the early post-stroke period are associated with an increased risk or death and the combined outcome of death/dependency. While the authors also suggested that a decrease in blood pressure between 8mmHg and 14.6mmHg was associated with the lowest odds of poor outcome (death, dependency and intracerebral hemorrhage), the results were not statistically significant. (Geeganage & Bath, 2009).

For patients treated with thrombolysis, reductions in blood pressure may be indicated, when elevations are extreme (eg., SBP ≥220 mm Hg or DBP≥120 mm Hg). Using the results of 11080 patients included in the SITS-ISTR study who were treated with thrombolysis, Ahmed et al (2009) reported that high systolic BP, 2 to 24 hours after thrombolysis was associated with worse outcome (p>0.001). Blood pressures greater than 170 mmHg were associated with higher odds of death, dependency and subsequent hemorrhage compared to blood pressures between 141 and 150 mmHg. The results from the blood pressure-lowering arm of the ENCHANTED trial, when released, will provide additional information to guide patient management.

Glucose Management

Baseline hyperglycemia has been identified as independent predictor of poor stroke outcome and may be a marker of increased stroke severity. The presence of hyperglycemia may be of particular concern

among patients without a history of premorbid diabetes. Using patient data from the ECASS II trial, Yong & Kaste (2008) examined the association between stroke outcomes and four patterns of serum glucose over the initial 24-hour period post stroke. Among 161 patients with pre-morbid diabetes, the odds of poor outcome were not increased significantly for patients with persistent hyperglycemia, or among patients with hyperglycemia at 24 hours, compared with patients with persistent normoglycemia. However, among 587 non-diabetics, patients with persistent hyperglycemia experienced significantly worse outcomes compared to those with persistent normoglycemia. The odds of a good functional outcome at 30 days, minimal disability at 90 days or neurological improvement over 7 days were significantly reduced compared with patients with persistent normoglycemia, while the odds of 90-day mortality and parenchymal hemorrhage were increased significantly. Since initial hyperglycemia has been associated with poor stroke outcome, several trials have evaluated the potential benefit of tight blood glucose control early following stroke. The largest such study was the GIST-UK trial (Gray et al. 2007) in which 899 patients were randomized to receive variable-dose-insulin glucose potassium insulin (GKI) to maintain blood glucose concentration between 4-7mmol/L or saline (control) as a continuous intravenous infusion for 24 hours. For patients in the control group, if capillary glucose > 17 mmol/L, insulin therapy could be started, at the discretion of the treating physician. Treatment with GKI was not associated with a significant reduction in 90-day mortality (OR= 1.14; 95% CI 0.86 to 1.51; p=0.37) or the avoidance of severe disability (OR= 0.96; 95% CI 0.70 to 1.32). Rescue dextrose was given to 15.7% of GKI-treated patients for asymptomatic prolonged hypoglycemia. The trial was stopped prematurely due to slow enrolment. More recently, Rosso et al. (2012) randomized 120 patients to receive intravenous administration of insulin (IIT) on a continuous basis or subcutaneous administration (every 4 hours) for 24 hours (SIT). The stop point for treatment was <5.5 mmol/L in the IIT group and 8 mmol/L in the SIT group. Although a significantly higher number of patients in the IIT group achieved and maintained a mean blood glucose level of <7mmol/L, the mean size of infarct growth was significantly higher among patients in the IIT group (27.9 vs. 10.8 cm^3, p=0.04), there were significantly more asymptomatic hypoglycemia events among patients in the IIT group (8 vs. 0, p=0.02) and there was no significant difference in the number of patients who experienced a good outcome (45.6% vs. 45.6%) or death (15.6% vs. 10.0%) at 3 months. In a Cochrane review (Bellolio et al. 2014) used the results of 11 RCTs including 1583 adult patients with blood glucose level of > 6.1mmol/L obtained within 24 hours of stroke, Blood-glucose-lowering treatment was not associated with reductions in death or dependency (OR=0.99, 95% CI 0.79-1.2) or final neurological deficit, but treatment did increase the risk of was associated symptomatic and asymptomatic hypoglycemia events.

References and Evidence Tables

Evidence Table 4 and References available on website at www.strokebestpractices.ca

Section Five: Acute Ischemic Stroke Treatment (Sixth Edition, 2018)

5. Acute Ischemic Stroke Treatment Recommendations

Box 5A Criteria for Stroke Centres Providing Acute Ischemic Stroke Treatment

Within the Canadian Stroke Best Practices Optimal Stroke Services Framework all hospitals in Canada have been identified as either comprehensive, advanced/primary, general non-stroke acute care hospitals, or basic healthcare facilities (generally small rural and remote sites). Comprehensive and advanced/primary stroke centres are those that have coordinated stroke care services, including CT imaging and alteplase administration available on-site.

Some comprehensive stroke centres and a select group of advanced/primary stroke centres will be able to provide endovascular thrombectomy (with mechanical embolectomy) for acute ischemic stroke. To provide endovascular thrombectomy, centres must meet the following criteria:

- A designated stroke team which includes physicians with stroke expertise (stroke neurologist or other physicians with advanced stroke training); stroke nurses and advanced practice nurses (and/or nurse practitioners); neurosurgeons; (neuro)-radiologists, Emergency Physicians; critical care physicians; rehabilitation therapists (physical therapists, occupational therapists, speech-language pathologists, and dieticians), pharmacists, and social workers.
- Neurointerventional expertise on-site with available 24-hour access, seven days a week.
- On-site neurosurgery support and neurocritical care services.
- Stroke imaging on-site with 24-hour access, seven days a week, including a computed tomography (CT) scanner (i.e. 3rd generation or higher helical scanner) with programming for CT angiography (CTA). Multiphase or dynamic CTA or CT perfusion (CTP) imaging can also be used if available on-site. MR imaging (MRI, MRA, MRP) may be considered if available on site and will not delay acute stroke treatments.
- Capability to administer intravenous alteplase;
- Designated stroke unit on-site – a geographically defined hospital unit dedicated to the care of stroke patients, with protocols in place that follow current evidence-based stroke best practice recommendations for acute stroke management and early access to rehabilitation assessment and therapy.

5.1 Patient Selection for Acute Ischemic Stroke Treatments

*Note: treatment benefits from revascularization decreases over time as an estimated 1.9 million brain cells die every minute following stroke onset (Saver 2006); therefore, all patients with stroke **should be treated as fast as possible** to maximize potential for the best outcomes, and the new extended time windows should not be interpreted to mean that time to treatment can be slowed down in any way.*

i. All patients with *disabling* acute ischemic stroke within 24 hours of stroke symptom onset or last known well should be rapidly screened clinically and with neurovascular imaging [Evidence Level B].

ii. All patients with *disabling* acute ischemic stroke who can be treated within the indicated time windows must be screened *without delay* by a physician with stroke expertise (either on-site or by telemedicine/telestroke consultation) to determine their eligibility for both intravenous alteplase (**within 4.5 hours** from stroke symptom onset) and/or interventional treatment with endovascular

thrombectomy (**within a 6 hour** window from stroke symptom onset). [Evidence Level A].

iii. Patients meeting criteria in 5.1 (i) (within 6 hours) should immediately undergo neurovascular imaging with non-contrast computed tomography (NCCT) and including CT angiography (CTA) then considered for treatment on the basis of imaging [Evidence Level A].

iv. There are randomized controlled trials which indicate that **highly selected** patients with disabling stroke symptoms may benefit from endovascular thrombectomy **up to 24 hours** from the time they were last known well, including patients with stroke on awakening, and patients should be considered for eligibility within the extended time window on a case-by-case basis [Evidence Level A]. *Note, these patients were selected using CTP or diffusion-weighted criteria (as defined in Box 5C below)* (new for 2018)

v. Highly selected patients being considered for endovascular thrombectomy beyond 6 hours will require additional advanced neurovascular imaging [Evidence Level A]. *Refer to Box 4D for additional Imaging Selection Criteria.*

Clinical considerations:

1. One recent multi-centre randomized double-blind placebo controlled trial compared alteplase to placebo for ischemic stroke patients with unknown time of onset, using MRI selection criteria (DWI/FLAIR mismatch). It included ischemic stroke patients who were not candidates for endovascular thrombectomy, and who would otherwise have met the criteria for acute intravenous alteplase administration [46] (*refer to Box 5B for alteplase criteria*)
   - This trial demonstrates a clinical benefit of intravenous alteplase administered more than 4.5 h from the time the patient was last known well in patients where onset time is unknown (no upper time limit defined).
   - If intravenous alteplase is considered after 4.5 h, a consultation with a physician with stroke expertise should be obtained. Selection of patients for intravenous alteplase in patients presenting **after 4.5 hours** on the basis of CT, CTA and CTP remains unproven at this time.
   - *MRI scanning can be challenging to obtain urgently in an Emergency Department setting. This must be considered in decision-making and not delay decisions regarding endovascular thrombectomy eligibility.*

5.2 Imaging Criteria

Refer to Section 4.2 for detailed recommendations and Boxes 4A, 4B, 4C and 4D for selection criteria for neuroimaging.

i. Patients should be considered for revascularization treatment when there is no evidence of extensive early infarct changes [Evidence Level B], in consultation with physicians with stroke expertise. *Note: one possible tool to assess infarct change is the ASPECT score: www.aspectsinstroke.com*

   a. Timely access to CT or MR perfusion scanning can also be used to demonstrate a perfusion mismatch and to determine the extent of the ischemic core [Evidence Level A], especially in patients beyond 6 hours from last known well, including patients with stroke on awakening.

ii. For endovascular thrombectomy, patients should have a proximal occlusion in the anterior circulation [Evidence Level A]. *Refer to Box 5C for endovascular thrombectomy inclusion and exclusion criteria.*

5.3 Intravenous Thrombolysis with Alteplase

i. All eligible patients with disabling ischemic stroke should be offered intravenous alteplase [Evidence Level A]. Eligible patients are those who can receive intravenous alteplase within 4.5 hours of the onset of stroke symptoms [Evidence Level A]. *Refer to Section 4.2 and Boxes 4A – 4D for detailed recommendations on neuroimaging; Refer to Box 5B for inclusion and exclusion criteria for intravenous alteplase eligibility. Refer to Section 5.1 Clinical Considerations for patients who arrive beyond the 4.5 hour time window.*

   a. When it is unclear whether or not a patient should be treated with alteplase, urgently consult with a stroke specialist within the institution or through telestroke services [Evidence Level C].

   b. If there is uncertainty regarding CT imaging interpretation, consult a radiologist in your institution [Evidence Level C].

ii. All eligible patients should receive intravenous alteplase as soon as possible after hospital arrival [Evidence Level A], with a target door-to-needle time of less than 60 minutes in 90% of treated patients, and a median door-to-needle time of 30 minutes [Evidence Level B].

   a. Treatment should be initiated as soon as possible after patient arrival and CT scan [Evidence Level B]; every effort should be made to ensure door-to-needle times are routinely monitored and improved [Evidence Level C].

   b. Alteplase should be administered using a dose of 0.9 mg/kg to a maximum of 90 mg total dose, with 10 percent (0.09 mg/kg) given as an intravenous bolus over one minute and the remaining 90 percent (0.81 mg/kg) given as an intravenous infusion over 60 minutes [Evidence Level A].

      Caution: the dosing of alteplase for stroke is not the same as the dosing protocol for administration of alteplase for myocardial infarction.

iii. **Hospital inpatients** who present with a sudden onset of new stroke symptoms should be rapidly evaluated by a specialist team and provided with access to appropriate acute stroke treatments (including thrombolysis and endovascular thrombectomy) [Evidence Level B]. *Note: once stroke occurs to an existing inpatient, all other sections of the Canadian Stroke Best Practice modules apply to these patients for assessment, diagnosis, management, and recovery.*

iv. Management of complications from alteplase administration:

   a. For patients with angio-edema, a staged response using antihistamines, glucocorticoids and standard airway management should be used as per local protocol [Evidence Level C].

   b. There is insufficient evidence to support the routine use of cryoprecipitate, fresh frozen plasma, prothrombin complex concentrates, tranexamic acid, factor VIIa, or platelet transfusions for alteplase - associated bleeding [Evidence Level C]. Use of these medications should be decided on an individual case basis.

Clinical Considerations for Alteplase Administration: (new for 2018)

1. Consent – Intravenous thrombolysis and endovascular therapy are considered the standard of care for acute stroke treatment. Routine procedures for emergency consent apply.
2. Intravenous alteplase is considered the standard of care and is currently the only approved thrombolytic agent for acute ischemic stroke treatment. There are other drugs being investigated; however, at this time are not approved for use in stroke patients.
3. Alteplase administration for patients on direct oral anticoagulants (DOACs): alteplase should **not** routinely be administered to patients on DOACs presenting with acute ischemic stroke. Endovascular thrombectomy may be considered in in these cases for eligible patients, and decisions should be based on individual patient factors and assessment of benefit and risk.

a. In comprehensive stroke centres with access to specialized tests of DOAC levels and reversal agents, thrombolysis could be considered, and decisions should be based on individual patient characteristics, in consultation with hematology specialists, patients and their families.

4. There remain situations in which clinical trial data to support the use of intravenous thrombolytic therapy is more limited. In these situations urgent consultation with a stroke expert is recommended alongside the clinical judgment of the treating physician and discussion with the patient or substitute decision maker.

    a. This may apply to: pediatric stroke (newborn to age 18 years); and pregnant women who experience an acute ischemic stroke. *Refer to Canadian Stroke Best Practices Management of Acute Stroke during Pregnancy Consensus Statement for further information*

5.4 Acute Endovascular Thrombectomy Treatment (EVT)

Refer to Section 4.2 and Boxes 4B, 4C and 4D for detailed recommendations on neuroimaging-based selection criteria.

i. Endovascular thrombectomy should be offered within a coordinated system of care including agreements with emergency medical services, access to rapid neurovascular (brain and vascular) imaging, coordination between emergency medical services, the Emergency Department, the stroke team and radiology, local expertise in neurointervention, and access to a stroke unit for ongoing management [Evidence Level A].

ii. Endovascular thrombectomy is indicated in patients based upon imaging selection with non-contrast CT head and CT angiography (including extracranial and intracranial arteries) [Evidence Level A]. *Refer to Box 5C for Inclusion Criteria for endovascular thrombectomy.*

iii. Endovascular thrombectomy is indicated in patients who have received intravenous alteplase and those who are not eligible for intravenous alteplase [Evidence Level A].

iv. Patients eligible for intravenous alteplase as well as endovascular thrombectomy should also be treated with intravenous alteplase, which can be initiated while simultaneously preparing the angiography suite for endovascular thrombectomy [Evidence Level A].

v. Eligible patients who can be treated with endovascular thrombectomy **within 6 hours** of symptom onset (i.e., arterial access within 6 hours of onset) should receive endovascular thrombectomy [Evidence Level A]. *Refer to Box 4B for Imaging Inclusion Criteria for endovascular thrombectomy.*

vi. **Highly selected patients** with large vessel occlusion who can be treated with endovascular thrombectomy **within 24 hours** of symptom onset (i.e., arterial access within 24 hours of onset) and those patients with stroke discovered on awakening should receive endovascular thrombectomy [Evidence Level A]. *Refer to Box 4C for Imaging Inclusion Criteria for endovascular thrombectomy beyond 6 hours from onset.*

vii. For large artery occlusions in the posterior circulation (e.g. basilar artery occlusion) the decision to treat with endovascular thrombectomy should be based on the potential benefits and risks of the treatment for the individual patient, and made by a physician with stroke expertise in consultation with the patient and/or substitute decision-makers. [Evidence Level C]. *Note: randomized trials are currently ongoing and guidance will be reviewed when trial results are available.*

viii. **Sedation:** For endovascular procedures, procedural sedation is generally preferred over general anaesthesia and intubation in most patients when necessary [Evidence Level B].

    a. General anaesthesia and intubation is appropriate if medically indicated (e.g. for airway compromise, respiratory distress, depressed level of consciousness, severe agitation, or any other indication determined by the treating physician) and in such cases, excessive and prolonged hypotension and time delays should be avoided [Evidence Level B].

Clinical Considerations for Endovascular Thrombectomy (new for 2018)

1. For patients transferred to an EVT-enabled hospital, in order to ensure patient remains a candidate for EVT, consider doing repeat NCCT immediately on arrival if most recent CT was completed more than 60 minutes prior to arrival at the EVT–enabled site.
2. Device selection should be at the discretion of the interventionalists based on clinical and technical factors during the procedure.
3. For patients undergoing EVT following administration of alteplase, there should not be a delay in proceeding to EVT to determine clinical effectiveness of alteplase.

Box 5B Criteria for Acute Thrombolytic Therapy with Intravenous Alteplase

Refer to Section 4.2 and Box 4A for detailed recommendations on neuroimaging-based selection criteria

These criteria are designed to guide clinical decision-making; however, the decision to use alteplase in these situations should be based on the clinical judgment of the treating physician. The relative benefits of alteplase therapy versus any potential risks or contraindications should be weighed on an individual basis.

IV alteplase Treatment Inclusion Criteria

- ❑ Diagnosis of ischemic stroke causing disabling neurologic deficit in a patient who is 18 years of age or older.
  - For adolescents, decision to administer alteplase should be based on clinical judgment, presenting symptoms, and patient age; and, if possible, consultation with a pediatric stroke specialist.
- ❑ Time from last known well (onset of stroke symptoms) less than 4.5 hours before alteplase administration. ** For patients beyond 4.5 hours refer to Section 5.1 Clinical considerations for more information.*

Absolute Exclusion Criteria

- ❑ Any source of active hemorrhage or any condition that could increase the risk of major hemorrhage after alteplase administration.
- ❑ Any hemorrhage on brain imaging.

Relative Exclusion Criteria (requiring clinical judgement based upon the specific situation)

Historical

- ❑ History of intracranial hemorrhage.
- ❑ Stroke or serious head or spinal trauma in the preceding three months.
- ❑ Major surgery, such as cardiac, thoracic, abdominal, or orthopedic in the preceding 14 days. Risk varies according to the procedure.
- ❑ Arterial puncture at a non-compressible site in the previous seven days.

Clinical

- ❑ Symptoms suggestive of subarachnoid hemorrhage.
- ❑ Stroke symptoms due to another non-ischemic acute neurological condition such as seizure with post-ictal Todd's paralysis or focal neurological signs due to severe hypo- or hyperglycemia.
- ❑ Hypertension refractory to aggressive hyperacute antihypertensive treatment such that target blood pressure less than 180/105 cannot be achieved or maintained. Blood pressure should be treated rapidly and aggressively in order to minimize delays to thrombolysis.

- ❑ Patient currently prescribed and taking a direct non-vitamin K oral anticoagulant (DOAC). *Refer to Section 5.2 clinical considerations for additional information.*

CT or MRI Findings

- ❑ CT showing early signs of extensive infarction

Laboratory

- ❑ Blood glucose concentration below 2.7 mmol/L or above 22.2 mmol/L.
- ❑ Elevated activated partial-thromboplastin time.
- ❑ International Normalized Ratio greater than 1.7.
- ❑ Platelet count below 100,000 per cubic millimetre.

Box 5C Inclusion Criteria for Endovascular Thrombectomy

Refer to Section 4.2 and Boxes 4B, 4C and 4D for detailed recommendations on neuroimaging-based selection criteria

1. If intravenous alteplase is given in conjunction with endovascular thrombectomy, refer to Box 5B for additional inclusion criteria.
2. **Age**: Patients under 18 years of age. There is no current evidence for use of endovascular thrombectomy in pediatric populations and the decision to treat should be based on the potential benefits and risks of the therapy, made by a physician with Pediatric stroke expertise in consultation with the patient and/or family/substitute decision-makers.
3. **Premorbid Condition Criteria**: In general, functionally independent and life expectancy greater than 3 months.
4. **Imaging:**
    a. A small-to-moderate ischemic core (such as with ASPECTS score of 6 or higher).
        - For patients with large ischemic core, such as with ASPECTS score less than 6, the decision to treat should be based on the potential benefits and risks of the treatment, made by a physician with stroke expertise in consultation with the neuro-interventionalist, and patient and/or family/substitute decision-makers.

    b. Intracranial artery occlusion in the anterior circulation, including proximal large vessel occlusions in the distal ICA or MCA and immediate branches.

    c. For patients with basilar artery occlusions, the decision to treat with endovascular thrombectomy should be based on the potential benefits and risks of the therapy, made by a physician with stroke expertise in consultation with the neuro-interventionist, and the patient and/or decision-makers.
5. **Time to treatment:** The decision to proceed with endovascular thrombectomy should be shared between the physician with clinical stroke expertise and the neuro-interventionalist, who will make use of the available imaging information as is indicated. Details regarding imaging parameters commonly used in the literature are included in Box 5B-D.
    a. Specifically:
        i. Patients should have immediate neurovascular imaging (see above) to determine eligibility. Patients can be considered for imaging within a 24-hour window from stroke onset or last known well.
        ii. For patients presenting less than 6 hours from onset of stroke symptoms or last

known well to initiation of treatment (i.e. arterial puncture), all patients who meet eligibility criteria should be treated.

iii. For patients presenting between 6 to 24 hours from last seen well, highly selected patients may be treated if they meet clinical and imaging criteria, and based on local protocols and available expertise in endovascular thrombectomy.

Rationale

Meta-analyses of the randomized controlled trials of intravenous alteplase for acute ischemic stroke have shown that thrombolytic treatment can reduce the risk of disability and death, despite the risk of serious bleeding. The latest time for alteplase administration after stroke onset remains imprecisely defined, but currently available data show clear evidence of benefit when given up to 4.5 hours after the onset of symptoms. The available evidence demonstrates a strong inverse relationship between treatment delay and clinical outcome; eligible patients should be treated without delay, regardless of when they present within the treatment window.

Endovascular treatment for large artery ischemic stroke has clearly demonstrated efficacy with numbers needed to treat (NNT) of approximately four to achieve functional independence at 90 days. Recent data from the DAWN trial (Nogueira et al. 2017) suggest the NNT may be as low as three, while pooled results from a series of older trials, indicated the number was higher, closer to five (HERMES, Goyal et al. 2016). This therapy has profound impact on patients who suffer the most devastating ischemic strokes; patients who, if left untreated, will place a more significant burden on the healthcare system, long term care and family caregivers.

(Note: o obtain mRS of 0-2 at 90 days (49% vs. 13%=NNT of 2.8); HEREMES 2016 meta-analysis to obtain mRS score of 0-2 at 90 days (46% vs. 26.5%=NNT of 5.1))

System Implications

1. Local protocols should prioritize stroke patients for immediate access to appropriate diagnostics such as CT imaging and neurovascular imaging with CTA. This should include patients with known times of stroke symptom onset (or time last seen well), and patients who are discovered with stroke symptoms on wakening.
2. Coordinated and integrated systems of care involving all relevant personnel in the prehospital and emergency care of stroke patients, including paramedics, Emergency Department staff, stroke teams, radiologists and neurointerventionists. Protocols should be in place in partnership with EMS agencies and treating hospitals, and between hospitals within stroke systems to ensure rapid transport to centres providing advanced stroke services within treatment time windows
3. Considerations should be given to northern, rural, remote and Indigenous residents to ensure immediate access to appropriate diagnostics and treatment is not delayed.
4. Health regions and stroke systems should examine and determine the possible resource impact of the EVT time window extension (up to 24 hours in highly selected cases). Demand for imaging will increase especially at comprehensive stroke and EVT-enabled centres. Staffing, service hours and capacity should be considered to ensure efficiency and effectiveness of services.
5. System planners and patient flow specialists should plan for significant challenges associated with diversion of potential EVT candidates to EVT-enabled centres. This will affect Emergency Departments, Radiology Departments and acute inpatient units, where occupancy rates are already stretched (over 100% in many hospitals).
6. Stroke neurology and neurointerventional expertise should be regionalized, with a system in place across regions for rapid access to physicians experienced in acute thrombolysis and endovascular therapies, including through telemedicine. This includes protocols for contacting physicians with stroke expertise for administration of intravenous alteplase, as well as transport to

higher levels of stroke care, as needed, for intravenous alteplase or endovascular thrombectomy.

7. Build capacity for trained neurointerventionists within health regions and academic institutions to ensure sufficient availability to meet regional and provincial EVT healthcare needs.
8. Hyperacute protocols in place and well-communicated to all healthcare practitioners within the hospital regarding management of in-hospital stroke patients, ensuring access to CT imaging of the brain and CTA of the extracranial and intracranial vessels as soon as possible after stroke symptom onset.
9. Access to specialized acute stroke units where staff are experienced in managing patients who have received alteplase or endovascular thrombectomy.
10. Endovascular interventional programs are in evolution across Canada; decisions around appropriate site, transfer and bypass protocols, and timelines will be determined at the provincial or regional level. Decisions about when those services are fully operational, and who should be transferred by paramedics to those facilities should be made at the provincial/regional level and communicated to all relevant stakeholders.
11. Availability of helical CT scanners with appropriate programming for CT angiography (multiphase or dynamic CTA) and CT perfusion sequences, and appropriate post-processing software optimized for the production of high-quality imaging.
12. A consistent, comprehensive data collection protocol for EVT across Canada should be established to monitor patient outcomes.

Performance Measures

1. **Overall proportion of all ischemic stroke patients who receive treatment with intravenous alteplase (core).**
2. Median time (in minutes) from patient arrival in the Emergency Department to administration of intravenous alteplase.
3. Median time from hospital arrival to groin puncture, and from CT scan (first slice of the non-contrast CT) to groin puncture for patients undergoing endovascular thrombectomy.
4. Proportion of ischemic stroke patients who receive treatment with intravenous alteplase within 3.0 and 4.5 hours of symptom onset.
5. Proportion of all thrombolyzed stroke patients who receive alteplase within 30 minutes of hospital arrival (core).
6. **Overall proportion of all ischemic stroke patients who receive treatment with endovascular thrombectomy (core).**
7. Median time from hospital arrival to first reperfusion for patients undergoing endovascular thrombectomy. Time of first reperfusion is defined as the first angiographic image showing partial or complete reperfusion of the affected arterial territory (* CIHI project 440 Indicator).
8. For patients with stroke while in hospital for other medical reasons (in-hospital strokes), median time from last known well to brain imaging.
9. For patients with stroke while in hospital for other medical reasons (in-hospital strokes), median time from last known well to acute thrombolysis or endovascular thrombectomy (groin puncture).
10. Final reperfusion status for patients undergoing endovascular reperfusion therapy, quantified using the modified Thrombolysis in Cerebral Infarction (mTICI) system. (* CIHI 440 Indicator)
11. Proportion of patients with symptomatic subarachnoid or intracerebral hemorrhage following intravenous alteplase (defined as any PH1, PH2, RIH, SAH, or IVH associated with a four-point or more worsening on the NIHSS within 24 hours).
12. Proportion of patients with symptomatic subarachnoid or intracerebral hemorrhage following endovascular thrombectomy (defined as any PH1, PH2, RIH, SAH, or IVH associated with a four-point or more worsening on the NIHSS within 24 hours).

13. Proportion of patients in rural or remote communities who receive alteplase through the use of telestroke technology (as a proportion of all ischemic stroke patients in that community and as a proportion of all telestroke consults for ischemic stroke).
14. Modified Rankin Scale (mRS) score of all stroke patients who receive intravenous alteplase or endovascular thrombectomy at time of hospital discharge and at 90 days post-hospital discharge.
15. In-hospital mortality rates (overall and 30-day) for ischemic stroke patients stratified by those who receive alteplase or endovascular thrombectomy and those who do not.

Measurement Notes

a. Refer to Core Indicator Reference Document for indicator calculations, all process timelines and outcome measures for intravenous acute thrombolysis and EVT.
b. In 2018, the Canadian Institute of Health Information is launching a new stroke quality of care special project (#440) as part of the Discharge Abstract Database extraction that enables data collection on six performance measures for endovascular thrombectomy. Identified above with * (CIHI Stroke Special Project for EVT440)
c. Data may be obtained from patient charts, through chart audit or review.
d. Time interval measurements should be taken from the time the patient is triaged or registered at the hospital (whichever time comes first) until the time of alteplase administration noted in the patient chart (nursing notes, Emergency Department record, or medication record).
e. For performance measures 4 and 5, calculate all percentiles and examine 50th and 90th percentiles and inter-quartile range.
f. When recording if alteplase is given, include times for both the administration of the bolus, and the time when the infusion is started – there are often delays between bolus and infusion which may decrease alteplase efficacy. The route of administration should also be recorded, as there are different times to administration benchmarks for intravenous and endovascular routes
g. For endovascular thrombectomy, treatment time should be time of first groin puncture.

Implementation Resources and Knowledge Translation Tools

Health Care Provider Information

- Canadian Stroke Best Practices Appendix Three: Screening and Assessment Tools for Acute Stroke Severity
- HSF Stroke Assessment and Prevention Pocket Cards 2017. Hard copy available through HSF order form
- Canadian Stroke Best Practices Management of Acute Stroke during Pregnancy Consensus Statement for further information
- Refer to Box 5A for Criteria for Stroke Centres Providing Acute Ischemic Stroke Treatment
- Refer to Box 5B for Inclusion and exclusion criteria for intravenous alteplase eligibility.
- Refer to Box 5C for Inclusion Criteria for endovascular therapy
- HSF Stroke Assessment Pocket Cards http://www.strokebestpractices.ca/wp-content/uploads/2017/07/002-17_CSBP_StrokeAssessPocketGuide_7.5x4.25_EN_v6_LR.pdf
- American College of Chest Physicians (ACCP) Anticoagulation Guidelines: http://www.chestnet.org/Guidelines-and-Resources
- Heart and Stroke Foundation Position Statement “Access to Medicine, Heart Disease and Stroke”: http://www.heartandstroke.ca/-/media/pdf-files/canada/2017-position-statements/accessto-medicine-ps-eng.ashx?la=en&hash=F9A97F0D9E2A708E3AC20F2EAFA6631C2510605A

- ASPECTS information: http://www.aspectsinstroke.com/

Patient Information

- "Taking Charge of Your Stroke Recovery: A survivor's guide to the Canadian Stroke Best Practice Recommendations": http://www.strokebestpractices.ca/wp-content/uploads/2014/08/HSF_SBP_PatientsGuide_F14_EN_July2014-FINAL.pdf
- "Your Stroke Journey": http://www.strokebestpractices.ca/wp-content/uploads/2015/03/YOURSTROKEJOURNEY.FINAL_.ENGLISH..pdf
- Post-Stroke Checklist: http://www.strokebestpractices.ca/wp-content/uploads/2014/06/HSF%20Post%20Stroke%20Checklist_WEB.pdf

Summary of the Evidence 2018f

Intravenous Thrombolysis

The weight of evidence from many large, international trials over a time frame of 20 years, clearly indicate that treatment with intravenous alteplase reduces the risk of death or disability following ischemic stroke, at 3 to 6 months post treatment. The NINDS trial (1995) was one of the earliest, large trials, which was conducted in the USA. Patients were randomized to receive alteplase or placebo within 3 hours of symptom onset. At 3 months, significantly more patients in the rt-PA group had experienced a good outcome (using any one of the study's 4 metrics), with no difference in 90-day mortality between groups. In contrast, patients who received alteplase within 3 to 5 hours in the ATLANTIS trial (1999) were no more likely to have a good neurological or functional outcome at 90 days than patients in the placebo group.

In the first ECASS trial (1995) 620 patients received alteplase or placebo within 6 hours of event. Using intention-to-treat analysis and including the data from 109 patients with major protocol violations, the authors did not report a significant benefit of treatment. The median Barthel Index and modified Rankin scores at 90 days did not differ between groups. In an analysis restricted to patients in the target population, there were differences favouring patients in the alteplase group. In the ECASS II trial (1998), there was again no significant difference on any of the primary outcomes. The percentages of patients with a good outcome at day 90 (mRS<2) treated with alteplase and placebo were 40.3% vs. 36.6%, respectively, absolute difference =3.7%, p=0.277. In subgroup analysis of patients treated < 3 hours and 3-6 hours, there were no between-group differences on any of the outcomes. The authors suggested that the reason for the null result may have been that the study was underpowered, since it was powered to detect a 10% difference in the primary outcome, but the observed difference between groups in previous trials was only 8.3%. Finally, in the ECASS III trial (2008) 821 patients were randomized within 3 and 4.5 hours of symptom onset. In this trial, a higher percentage of patients in the alteplase group experienced a favourable outcome, defined as mRS scores <2 (52.4% vs. 45.2%, adjusted OR=1.34, 95% CI 1.02 to 1.76, p=0.04). A higher percentage of patients in the alteplase group also had NIHSS scores of 0 or 1, (50.2% vs. 43.2%, adjusted OR=1.33, 95% CI 1.01 to 1.75, p=0.04). Secondary outcomes of the ECASS III trial were reported by Bluhmki et al. (2009). At 90 days, there were no between-group differences in the percentages of patients with mRS score of 0-2 (59% vs. 53%, p=0.097) or BI score ≥85 (60% vs. 56%, p=0.249, but a significantly greater percentage of patients had improved NIHSS scores of ≥8 points (58% vs. 51%, p=0.031). In all of the trials described above there was an increased risk of symptomatic ICH associated with treatment with alteplase and in some cases, increased short-term mortality; however, there were no differences between treatment and placebo groups in 90-day mortality.

The Third International Stroke Trial (2012), is the largest (n=3,035) and most recent trial of alteplase, in which patients were randomized to receive a standard dose of alteplase (0.9 mg/kg) or placebo. Investigators aimed to assess the risks and benefits of treatment among a broader group of patients, and to determine if particular subgroups of patients might benefit preferentially from treatment. In this trial, 95% of patients did not meet the strict licensing criteria, due to advance age or time to treatment. Unlike all previous, large trials, which excluded them, IST-3 included patients >80 years. In fact, the majority of patients (53%) were >80 years. Approximately one-third of all patients were treated within 0-3 hours, 3.0-4.5 hours and 4.5-6.0 hours of onset of symptoms. Overall, there was an increase in the risk of death within 7 days in patients who had received alteplase, although there was no difference in 6-month mortality in both crude and adjusted analyses. There was no significant difference in the percentage of patients who were treated with alteplase who were alive and independent (defined as an Oxford Handicap Score of 0-1) at 6 months (37% vs. 35%, adjusted OR=1.13, 95% CI 0.95 to 1.35, p=0.181, although a secondary ordinal analysis suggested a significant, favourable shift in the distribution of OHS scores at 6 months. Significantly improved odds of a good outcome at 6 months were associated with the sub groups of older patients (≥80 years), higher NIHSS scores, higher baseline probability of good outcome and treatment within 3 hours. Fatal or non-fatal symptomatic intracranial hemorrhage within 7 days occurred more frequently in patients in the t-PA group (7% vs. 1%, adjusted OR=6.94, 95% CI 4.07 to 11.8, p<0.0001). The 3-year risk of mortality (2016) was similar between groups (47% vs. 47%, 95% CI 3.6%, 95% CI -0.8 to 8.1); however, patients who received rt-PA had a significantly lower risk of death between 8 days and 3 years (41% vs. 47%; HR= 0.78, 95% CI 0·68–0·90, p=0·007).

Although it is known that the optimal timing of administration of intravenous alteplase is <3 hours, debate continues as to the safety and efficacy of treatment provided between 3 and 6 hours post stroke. The results from a few studies suggest that treatment is still beneficial if provided beyond the 3-hour window. The Safe Implementation of Treatment in Stroke-International Stroke Thrombolysis Registry (SITS-ISTR) includes patients who were treated with intravenous alteplase under strict licensing criteria and also those who were thought to be good candidates based on clinical/imaging assessment of the treating facility. Wahlgren et al. (2008) used data from a cohort of patients collected from 2002-2007 to compare the outcomes of patients who had been treated with alteplase within 3 hour of symptom onset (n=11,865) and those treated from 3-4.5 hours (n=644). The primary focus of this analysis was to assess treatment safety beyond the 3-hour treatment window. Patients in the <3-hour group had significantly lower initial median NIHSS scores (11 vs. 12, p<0.0001). There were no significant between group differences on any of the outcomes (symptomatic ICH within 24-36 hours, mortality within 3 months, or percentage of patients who were independent at 3 months); however, there was a trend towards increased number of patients treated from 3 to 4.5 hours who died (12.7% vs. 12.2%, adjusted OR=1.15, 95% CI 1.00-1.33, p=0.053) and who experienced symptomatic ICH (2.2% vs. 1.6%, adjusted OR=1.32, 95% CI 1.00-1.75, p=0.052). Additional analysis from the SITS-ISTR cohort was conducted to further explore the timing of alteplase treatment (Ahmed et al. 2010). In this study, patients treated within 3 hours (n=21,566) and 3-4.5 hours (n=2,376) of symptom onset between 2007 and 2010, were again compared. Significantly more patients treated from 3-4.5 hours experienced a symptomatic ICH (2.2% vs.1.7%, adjusted OR=1.44, 95% CI 1.05-1.97, p=0.02), and were dead at 3 months (12.0% vs. 12.3%, adjusted OR=1.26, 95% CI 1.07-1.49, p=0.005). Significantly fewer patients treated from 3-4.5 hours were independent at 3 months: (57.5% vs. 60.3%, adjusted OR=0.84, 95% CI 0.75-0.95, p=0.005). Emberson et al. (2014) used data from 6,756 patients from 9 major t-PA trials (NINDs a/b, ECASS I/II, III, ATLANTIS a/b, EPITHET, IST-3) to more closely examine the effect of timing of administration. Earlier treatment was associated with the increased odds of a good outcome, defined as an (mRS score of 0-1 (≤3.0 h: OR=1.75, 95% CI 1.35-2.27 vs. >3 to ≤4.5 h: OR=1.26, 95% CI 1.05-1051 vs. >4.5 h: OR=1.15, 95% CI 0.95-1.40). Framed slightly differently, when patient-level data from the same 9 major RCTs were recently pooled, Lees et al. (2016) reported

that for each patient treated within 3 hours, significantly more would have a better outcome (122/1,000, 95% CI 16-171), whereas for each patient treated >4.5 hours, only 20 patients/1,000 (95% CI -31-75, p=0.45) would have a better outcome. Wardlaw et al. (2013), including the results from 12 RCTs (7,012 patients), concluded that for every 1,000 patients treated up to 6 hours following stroke, 42 more patients were alive and independent (mRS<2) at the end of follow-up, despite an increase in early ICH and mortality. The authors also suggested that patients who did not meet strict licensing criteria due to age and timing of treatment (i.e., patients from the IST-3) trial were just as likely to benefit; however, early treatment, within 3 hours of stroke onset, was more effective. Most recently, the results from the Efficacy and Safety of MRI-based Thrombolysis in Wake-up Stroke (WAKE-Up) trial (Thomalla et al. 2018) suggest that highly-selected patients with mild to moderate ischemic strokes and an unknown time of symptom onset, treated with alteplase may also benefit from treatment. Patients in this trial were not eligible for treatment with mechanical thrombectomy and were selected based on a pattern of "DWI-FLAIR-mismatch. A significantly higher proportion of patients in the alteplase group had a favourable clinical outcome (mRS 0-1) at 90 days (53.3% vs. 41.8%, adj OR=1.61, 95% CI 1.06-2.36, p=0.02), although the risk of parenchymal hemorrhage type 2 was significantly higher compared with placebo (4% vs. 0.4%, adj OR=10.46, 95% CI 1.32 to 82.77, p=0.03).

The standard treatment dose of rt-PA is established to be 0.9 mg/kg, with a maximum dose of 90 mg. The non-inferiority of a lower dose (0.6 mg/kg) was recently examined in the Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED) trial (Anderson et al. 2016). The primary outcome (death or disability at 90 days) occurred in 53.2% of low-dose patients and 51.1% in standard dose patients (OR=1.09, 95% CI 0.95-1.25, p for non-inferiority=0.51), which exceeded the upper boundary set for non-inferiority of 1.14. The risks of death within 90 days or serious adverse events did not differ significantly between groups (low dose vs. standard dose: 8.5% vs. 10.3%; OR=0.80, 95% CI 0.63-1.01, p=0.07 and 25.1% vs. 27.3%; OR=0.89, 95% CI 0.76-1.04, p=0.16, respectively), although the risk of symptomatic ICH was significantly higher in patients that received the standard dose of rt-PA.

Although not yet approved in Canada for the use in stroke, results from several recent studies, indicate that tenecteplase, which has some pharmacokinetic advantages over alteplase, may be non-inferior to alteplase. In the *NOR-TEST* Logallo et al. (2017) recruited 1,100 patients from 13 stroke units. Patients were randomized to receive intravenous tenecteplase 0.4 mg/kg (maximum of 40 mg) or alteplase 0.9 mg/kg (maximum of 90 mg). At 90 days, a similar proportion of patients had an excellent outcome (mRS 0-1, 64% vs. 63%). Similar percentages of patients in each group experienced an ICH within 24-48 hours (9%) and had died by 90 days (5%). Results from the phase II *ATTEST* Trial, (Huang et al. 2015) also suggest that tenecteplase is non-inferior to alteplase. In this trail, 104 patients were randomized to receive tenecteplase (0.25 mg/kg, 25 mg max) or alteplase (0.9 mg/kg, 90 mg max) within 4.5 hours of ischemic stroke. Safety and efficacy outcomes were non-significantly different between groups.

The use of mobile stroke units, ambulances which are equipped with specialized equipment, such as on-site laboratories and CT scanners, and are staffed with additional personnel with stroke expertise, are now appearing in large, urban cities. The feasibility and effectiveness of these vehicles has yet to be established. Kunz et al. (2016) compared the outcomes of patients who received thrombolysis therapy using the mobile stroke unit, STEMO from 2011-2015 with patients who received thrombolysis, but arrived at hospital via traditional emergency medical services. A significantly higher proportion of patients in the STEMO group were treated ≤ 90 minutes of stroke (62% vs. 35%, p<0.0005) and were living without severe disability at 3 months (83% vs. 74%, p=0.004). The 3-month mortality was also significantly lower in the STEMO group (6% vs. 10%, p=0.022). However, there was no significant difference in the primary outcome, the number of patients who achieved an excellent outcome (mRS 0-1) at 3 months (53%

STEMO vs. 47% conventional, p=0.14). There were no significant differences in the safety outcomes between the 2 groups (sICH 3% vs. 5%, p=0.27 and 7-day mortality 2% vs. 4%, p=0.23). Adjusting for baseline characteristics, STEMO was an independent predictor of living without severe disability at 3 months (OR=1.86, 95% CI 1.20-2.88, p=0.006), but not for the primary outcome (OR=1.40, 95% CI 1.00-1.97, p=0.052). In an earlier study examining the use of STEMO, (Ebinger et al. 2014), among patients for whom STEMO was deployed, the mean alarm-to-treatment time for patients who received thrombolysis was reduced by 25 minutes, compared with control weeks. Of the eligible patients, t-PA was used in 32.6% of STEMO deployment cases, 29% during STEMO weeks, and 21.1% during control weeks.

The use of thrombolytic therapy in patients who are younger than 18 years and in women at any stage of pregnancy has not been evaluated empirically. The evidence base for the safety and effectiveness of the use of thrombolysis during pregnancy and the puerperium is derived from a series of case reports. The results from a total of 15 previous cases (10 intravenous and 5 intra-arterial), in addition to the presentation of their own case were summarized by Tversky et al. (2016). The neurological outcomes of these women were described as similar to (non-pregnant) patients who met the eligibility criteria. Most of the women who experienced significant recovery went on to deliver healthy babies. The evidence in terms of thrombolytic treatment for patients <18 years comes primarily from the International Pediatric Stroke Study, (IPSS) an observational study (n=687) in which the outcomes of 15 children, aged 2 months to 18 years who received thrombolytic therapy (9 with intravenous Alteplase, 6 with intra-arterial Alteplase). Overall, at the time of hospital discharge, 7 patients were reported having no or mild neurological deficits, 2 had died and the remainder had moderate or severe neurological deficits. The Thrombolysis in Pediatric Stroke (TIPS) study (Amlie-Lefond et al. 2009) is currently recruiting subjects for 5-year, prospective cohort, open-label, dose-finding trial of the safety and feasibility of intravenous and intra-arterial t-PA to treat acute childhood stroke (within 4.5 hours of symptoms). The TIPS investigators are aiming to include 48 subjects.

Endovascular Therapy

Re-vascularization can also be achieved through mechanical dislodgement with specialized devices (+/- intra-arterial and/or intravenous rt-PA). To date, 10 major RCTs have been completed for which results have been published, in which endovascular therapies were compared with best medical management. Several trials are still ongoing, or have yet to report their findings. The recent results from most of these trials indicate that rapid endovascular therapy may be a safe and more effective treatment than intravenous rt-PA alone, for patients with anterior circulation ischemic strokes in selected regions, when performed within 6-12 hours of symptom onset.

In the largest trial, MR CLEAN (Berkhemer et al. 2014), included 500 patients who were ≥18 years, with a baseline NIHSS score of 2 or greater, and were treatable within 6 hours of stroke onset. Patients were randomized to receive endovascular treatment with rt-PA or urokinase, and/or mechanical treatment with retrievable stents, which were used in 81.5% of patients, or other available devices, versus best medical management. The median time from stroke onset to groin puncture was 260 minutes. The majority of patients in both groups were treated with intravenous t-PA (87.1% intervention group, 90.6% control group). There was a significant shift in the distribution towards more favourable mRS scores among patients in the intervention group at 90 days (adj common OR=1.67, 95% CI 1.21-2.30). The odds of both a good (mRS 0-2) and excellent (mRS 0-1) recovery at day 90 were also significantly higher among patients in the intervention group (adj OR=2.07, 95% CI 1.07-4.02 and adj OR=2.16, 95% CIU 1.39-3.38, respectively). Patients in the intervention group were more likely to show no evidence of intracranial occlusion on follow-up CTA (adj OR=6.88, 95% CI 4.34-10.94, n=394) and to have a lower median final

infarct volume (-19 mL, 95% CI 3-34, n=298). At two-year follow-up (van den Berg et al. 2017), the odds of an mRS score of 0-2 remained significantly higher in the intervention group (37.1% vs. 23.9%, adj OR= 2.21, 95% CI 1.30−3.73, p=0.003). The ESCAPE trial (Goyal et al. 2015) enrolled 316 patients ≥18 years, with stroke onset less than 12 hours, a baseline NIHSS score of > 5 and moderate-to-good collateral circulation. Patients were randomized to receive endovascular mechanical thrombectomy, using available devices or best medical management. The median time from stroke onset to first reperfusion was 241 minutes. 72.7% of patients in the intervention group and 78.7% of those in the control group received intravenous t-PA. The odds of improvement in mRS scores by 1 point at 90 days were significantly higher among patients in the intervention group (adj OR=3.2, 95% CI 2.0-4.7). The odds of good outcome (mRS score 0-2) at 90 days were also higher in the intervention group (adj OR=1.7, 95% CI 1.3-2.2), as were the odds of a NIHSS score of 0-2 and a Barthel Index score of 95-100 (adj OR=2.1, 95% CI 1.5-3.0 and 1.7, 95% CI 1.3-2.22, respectively). The risk of death was significantly lower in the intervention group (adj RR=0.5, 95% CI 0.-0.8). In neither MR CLEAN nor ESCAPE, was there an increased risk of symptomatic ICH associated with endovascular therapy. No interaction effects were found in subgroup analyses of age, stroke severity, time to randomization, or baseline ASPECTS in either of the trials.

The THRACE trial (Bracard et al. 2016) had broader eligibility criteria and included 414 patients aged 18-80 years with an occlusion in the intracranial carotid, the MCA (M1) or the upper third of the basilar artery with onset of symptoms <4 hours and NIHSS score of 10-25 at randomization. Patients were randomized to receive dual intravenous rt-PA therapy + intra-arterial mechanical clot retrieval with the Merci, Penumbra, Catch or Solitaire devices or treatment with IV rt-PA only. The median time from symptom onset to thrombectomy was 250 minutes. The odds of achieving mRS score of 0-2 at 90 days were increased significantly in the thrombectomy group (53% vs. 42.1%, OR=1.55, 95% CI 1.05-2.3, p=0.028, NNT=10). There were no significant differences between groups in the number of patients with symptomatic or asymptomatic hemorrhages at 24 hours. Three trials evaluated the efficacy of the use of a specific retriever device (Solitaire FR Revascularization Device). In the EXTEND IA trial (Campbell et al. 2015), there were no inclusion criteria related to stroke severity. Seventy patients ≥18 years, with good premorbid function and an anterior circulation acute ischemic stroke, with criteria for mismatch, who could receive intra-arterial treatment within 6 hours of stroke onset, were included. All patients received intravenous rt-PA, while 35 also underwent intra-arterial mechanical clot retrieval. A significantly greater proportion of patients in the endovascular group experienced early neurological improvement (80% vs. 37%, p<0.001), >90% reperfusion without ICH at 24 hours (89% vs. 34%, p<0.001) and were functionally independent at day 90 (71% vs. 40%, p=0.009). The SWIFT-PRIME trial (Saver et al. 2015) randomized 196 patients, aged 18-80 years with NIHSS scores of 8-29 with a confirmed infarction located in the intracranial internal carotid artery, MCA, or carotid terminus who could be treated within 6 hours of onset of stroke symptom, to receive intravenous rt-PA therapy + intra-arterial mechanical clot retrieval, or rt-PA only. The likelihood of successful reperfusion (>90%) at 27 hours was significantly higher in the endovascular therapy group (82.8% vs. 40.4%, RR=2.05, 95% CI 1.45-2.91, p<0.001) and a significantly higher percentage of patients were independent at day 90 (mRS 0-2) (60.2% vs. 35.5%, RR=1.70, 95% CI 1.23-2.33, p=0.001). Finally, in the REVASCAT trial (Jovin et al. 2015), 206 patients with NIHSS scores of 6 or greater who could be treated within 8 hours of stroke onset were randomized to receive mechanical embolectomy + best medical management or best medical management only, which could include intravenous t-PA (78%). The odds of dramatic neurological improvement at 24 hours were increased significantly in the intervention group (adj OR=5.8, 95% CI 3.0-11.1). The odds for improvement by 1 mRS point at 90 days were increased significantly in the intervention group (adj OR=1.7, 95% CI 1.05-2.8), as were the odds of achieving an mRS score of 0-2 at 90 days (adj OR=2.1, 95% CI 1.1-4.0). At one-year follow-up (Davalos et al. 2017), the proportion of patients who were functionally independent (mRS score 0–2) was significantly higher for patients in the thrombectomy group

(44% vs. 30%; OR=1.86, 95% CI 95% CI 1.01-3.44). No treatment effects were noted based on sub group analyses in either SWIFT-PRIME or REVASCAT, based on age, baseline NIHSS score, site of occlusion, time to randomization, or ASPECTS score. There was no increased risk of symptomatic ICH in any of these trials.

Two trials (THERAPY and PISTE) halted recruitment prematurely following the presentation of the MR CLEAN trial, resulting in much smaller sample sized than planned. These trials generally reported improved outcomes for patients undergoing mechanical thrombectomy, although the smaller sample sizes were not powered to meet the primary endpoints. As a result, statistical significance was not always achieved.

The results of the DAWN (Nogueira et al. 2017) and DEFUSE-3 (Albers et al. 2018) trials suggest that the treatment window for mechanical thrombectomy is wider than previously thought. The DAWN trial included 206 patients, last been known to be well 6 to 24 hours earlier, with no previous disability (mRS 0-1) and who met clinical mismatch criteria who had either failed intravenous t-PA therapy, or for whom its administration was contraindicated, because of late presentation. Patients were randomized to treatment with thrombectomy with Trevo device + medical management or medical management alone. The trial was terminated early after interim analysis when efficacy of thrombectomy was established. The median intervals between the time that a patient was last known to be well and randomization was 12.2 hours in the thrombectomy group and 13.3 hours in the control group. The mean utility weighted mRS score was significantly higher in the thrombectomy group (5.5 vs. 3.4, adj difference =2.0, 95% Cr I 1.1-3.0, prob of superiority >0.999). There were no interactions in sub group analysis (mismatch criteria, sex, age, baseline NIHSS score, occlusion site, interval between time that patient was last known to be well and randomization and type of stroke onset). A significantly higher proportion of patients in the thrombectomy group experienced an early response to treatment, had achieved recanalization at 24 hours and were independent (mRS 0-2) at 90 days (49% vs. 13%, NNT=3). The admission criteria for the DEFUSE-3 trial were broader and included those who had remaining ischemic brain tissue that was not yet infarcted. The median time from stroke onset to randomization was just under 11 hours for patients in the endovascular group. A significantly higher proportion of patients in the endovascular group were independent (mRS 0-2) at 90 days (45% vs. 17%, OR=2.67, 95% CI 1.60–4.48, p<0.001, NNT=4).

The positive results from these 7 trials contrast with those of 3 earlier RCTs examining endovascular therapy using first generation devices, which are no longer on the market or in use in Canada. In the SYNTHESIS trial, Ciccone et al. (2013) randomized 362 patients to receive either pharmacological or mechanical thrombolysis, or a combination of these approaches or intravenous rt-PA within 4.5 hours of symptom onset. At 90 days, the percentages of patients alive, living without disability were similar between groups (30.4% vs. 34.8%, adjusted OR=0.71, 95% CI 0.44 to 1.14, p=0.16). The IMS III trial (Broderick et al. 2013), which also randomized patients to receive mechanical or pharmacological endovascular treatment, or intravenous t-PA was stopped early due to a lack of efficacy. Finally, the MR RESCUE trial (Kidwell et al. 2013). randomized 188 patients, within 8 hours of symptom onset to undergo mechanical embolectomy with the Merci Retriever or Penumbra System or standard care, grouped according to penumbra pattern vs. nonpenumbra pattern. At 90 days, there were no significant differences between groups (embolectomy vs. standard care) in the mean mRS score, the proportion of patients with a good outcome (mRS 0-2) or death among patients with penumbral or nonpenumbral patterns.

The results from several meta-analyses, indicated the odds of a favourable outcome were all significantly increased with mechanical thrombectomy. Goyal et al. (2016) included the results from 5 trials, using

second generation devices. The odds of achieving a mRS score of 0-1 or 0-2 at 90 days were significantly higher for patients in the endovascular group. The NNT for a one-point reduction in mRS was 2.6. Using data from these same trials, Saver et al. (2017) conducted pooled analysis to examine the timeframe in which endovascular treatment is associated with benefit. Compared with medical therapy, the odds of better disability outcomes at 90 days associated with endovascular therapy declined with longer time from symptom onset to arterial puncture. The point at which endovascular therapy was not associated with a significantly better outcome was 7 hours and 18 minutes. Campbell et al. (2016), included the results of 4 trials in which the Solitaire device was used. Treatment with Solitaire device was associated with both a significantly greater likelihood of independence, and of excellent functional outcome at 90 days compared with best medical management. Flynn et al. (2017) included the results from 8 trials and reported that mechanical thrombectomy was associated with significantly higher odds of functional independence (unadjusted OR=2.07, 95% CI 1.70-2.51, p<0.0001). Time series analysis demonstrated robust evidence for a 30% relative benefit for mechanical thrombectomy for this outcome. While there was no evidence that mechanical thrombectomy was associated with increased risks of mortality or symptomatic ICH, robust evidence to demonstrate a 30% relative risk reduction was lacking.

Evidence from several trials and meta-analyses have examined the outcomes of patients undergoing mechanical thrombectomy using general anesthesia versus conscious sedation. Generally, the findings indicate that conscious sedation is preferred. Using the results from 7 RCTs including MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, REVASCAT, PISTE and THRACE, Campbell et al. (2018) performed a patient-level meta-analysis comparing the outcomes of patients randomized to the mechanical thrombectomy groups who had received general anesthesia or non-general anesthesia. The odds of improved outcome using non-general anesthesia were significantly higher in ordinal analysis of mRS scores. The authors estimated for every 100 patients treated under general anesthesia (compared with non-general anesthesia), 18 patients would have worse functional outcome, including 10 who would not achieve functional independence. There was no increased risk of 90-day mortality associated with general anesthesia. The results from a meta-analysis including the results of 22 studies (Brinjikiji et al. 2017), also indicated that conscious sedation (i.e., non-general anesthesia) was associated with better outcomes. The odds of a favorable functional outcome at 90 days were significantly lower for patients who received general anesthesia (OR=0.58; 95% CI, 0.48–0.64), while the odds of 90-day mortality were significantly increased (OR=2.02, 95% CI 1.66–2.45). In contrast to these findings, Löwhagen Hendén et al. (2017) reported no significant differences between groups (general anesthesia vs conscious sedation) in the proportion of patients with a good outcome at 3 months (42% vs. 40%, p=1.00), or in the distribution of mRS scores at 90 days. In the SIESTA trial (Schönenberger et al. 2016), a significantly higher percentage of patients in the general anesthesia group had a good outcome (mRS 0-2) at 3 months (37% vs. 18.2%, p=0.01), compared with conscious sedation.

Many hospitals do not have the in-house expertise to perform endovascular procedures. As a result, patients who are potential candidates for treatment will need to be transported from receiving hospitals to a centre that provides interventional neuroradiologic services. Although the additional transportation involved will inevitably cause treatment delays, particularly the time from symptom onset to groin puncture, results from several recent studies suggest that patient outcomes may not be worse. Gerschenfeld et al. (2017) compared the outcomes of 159 patients who received mechanical thrombectomy following t-PA, using a drip and ship model and those who received the same procedure at the mother ship. Although the median process times from patients in the mothership group were all significantly shorter, there were no significant differences between groups in the proportion of patients with a favourable outcome (mRS 0-2) at 3 months, or who experienced a symptomatic ICH, and discharge NIHSS scores were similar. Weber et al. (2016) reported similar results in a study involving 643

patients consecutively admitted to 17 stroke units, 8 of which offered in-house endovascular procedures. Compared with stroke units which did not offer this service and were required to transfer patients to one that did, the frequency of in-hospital and 3-month mortality were similar. Median periprocedural times were significantly shorter for in-house group.

Reference List and Evidence Tables

Evidence Table 5A Acute Thrombolytic Therapy and 5B Endovascular thrombectomy and References available on website at www.strokebestpractices.ca

Section Six: Acute Antiplatelet Therapy (Sixth Edition, 2018)

6. Acute Antiplatelet Therapy Recommendations

Section Six: Recommendations for Acute Antiplatelet Therapy

i. All acute stroke patients not already on an antiplatelet agent and not receiving alteplase therapy should be given at least 160 mg of acetylsalicylic acid (ASA) immediately as a one-time loading dose after brain imaging has excluded intracranial hemorrhage and after dysphagia screening has been performed and passed. [Evidence Level A].

a. Acetylsalicylic acid (81 to 325 mg daily) should then be continued indefinitely or until an alternative antithrombotic regime is started [Evidence Level A]. *Refer to Canadian Stroke Best Practice Recommendations Prevention of Stroke Module Sections 6 and 7 for additional information on antithrombotic therapy*

ii. In very high risk TIA patients (*refer to Box 6A below and Section 2.1 for determination of very high risk patients* or per POINT trial criteria of $ABCD^2$ score > 4) or minor stroke of non cardioembolic origin (NIHSS 0-3), a combination of clopidogrel and acetylsalicylic acid should be given for a duration of 21 to 30 days followed by antiplatelet monotherapy (such as acetylsalicylic acid or clopidogrel alone) [Evidence Level A]. A minimal loading dose of 300 mg Clopidogrel (based on dose in CHANCE) up to 600mg (based on dose used in POINT) and 160 mg of acetylsalicylic acid should be given at the start of treatment [Evidence Level A]. [9, 57]

a. Dual antiplatelet therapy should be started as soon as possible after brain imaging, within 24 hours of symptom onset, and ideally within 12 hours.

b. Dual antiplatelet therapy should be started prior to discharge from the Emergency Department.

c. Patients should be counseled that dual antiplatelet therapy with aspirin and clopidogrel should continue for only 21-30 days. Patients should resume monotherapy after completion of dual therapy, and continue monotherapy indefinitely.

iii. In patients treated with tissue plasminogen activator (alteplase), initiation of antiplatelet agents should be delayed until after the 24-hour post-thrombolysis scan has excluded intracranial hemorrhage [Evidence Level B].

iv. In dysphagic patients, acetylsalicylic acid (80 mg daily) and clopidogrel (75 mg daily) may be given by enteral tube or acetylsalicylic acid by rectal suppository (325 mg daily) [Evidence Level A].

v. In pediatric patients, initial treatment with anticoagulation (heparin) or aspirin at established pediatric dosing should be considered and continued until cervical artery dissection and intracardiac thrombus is excluded. If neither is present, switch to acute aspirin therapy at dose of 1-5 mg/kg [Evidence Level B].

Refer to Canadian Stroke Best Practice Recommendations Secondary Prevention of Stroke module sections 6 and 7 for additional information on use of antithrombotic agents beyond the acute period

Clinical Considerations:

1. Patients with very high risk TIA or minor ischemic stroke caused by high-grade carotid stenosis who are candidates for urgent carotid endarterectomy or carotid stenting, should be reviewed with the interventionalist or surgeon to determine the appropriate timing and selection of antiplatelet agent(s). In some circumstances it may be appropriate to use aspirin monotherapy rather than dual antiplatelet therapy if carotid endarterectomy is planned urgently, to reduce peri-operative bleeding risk.
2. For patients on dual antiplatelet therapy, GI protection may be considered in patients at higher risk of GI bleeding [In POINT (90 day study) extracranial bleeding events were 0.9% in the dual antiplatelet therapy group and 0.4% in the monotherapy group; in CHANCE (21 day study) extracranial bleeding events were 0.3% in the dual antiplatelet therapy group and 0.3% in the monotherapy group.]

Box 6A:

VERY HIGH Risk for Recurrent Stroke (Symptom onset within last 48 Hours): Patients who present **within 48 hours** of a suspected transient ischemic attack or non-disabling ischemic stroke with the following symptoms are **considered at highest risk** of first or recurrent stroke: transient, fluctuating or persistent unilateral weakness (face, arm and/or leg); transient, fluctuating or persistent *language/speech disturbance; and/or* fluctuating or persistent symptoms *without motor weakness or language/speech disturbance* (e.g. hemibody sensory symptoms, monocular vision loss, hemifield vision loss, +/- other symptoms suggestive of posterior circulation stroke such as binocular diplopia, dysarthria, dysphagia, ataxia).

For additional risk stratification, refer to Section Two of this module.

Rationale

Acute-phase aspirin therapy reduces the risk of early recurrent ischemic stroke. Long-term aspirin therapy reduces the risk of ischemic stroke, myocardial infarction, and vascular death. There is a paucity of data from randomized controlled trials to support the use of other antiplatelet regimes in acute stroke patients. In clinical trials for alteplase, antithrombotic drugs (including aspirin) were avoided until after the 24-hour post-thrombolysis scan had excluded intracranial hemorrhage.

System Implications

1. Development and dissemination of protocols and standing order sets to guide initial management of ischemic stroke and transient ischemic attack patients
2. Pediatric awareness campaigns and education to healthcare professionals to optimize recognition of stroke and management.

Performance Measures

1. Proportion of ischemic stroke or TIA patients who receive acute aspirin therapy within the first 48 hours following symptom onset (core).
2. Median time from stroke patient arrival to hospital to administration of first dose of aspirin in hospital.

Measurement Notes

a. Time interval measurements should be taken from the time the patient is triaged or registered at the hospital (whichever time comes first) until the time the first dose is administered.

b. This indicator focuses on aspirin. Some centres may include other antiplatelet medications, such as clopidogrel or ASA combined with extended release dipyridamole. In cases where another agent is used instead of aspirin in the first 48 hours, this should be noted in the indicator definition.

c. Possible data sources include history and physical, physician's admission notes, nurses' admission notes, medication record.

Implementation Resources and Knowledge Transfer Tools

Health Care Provider Information

- Canadian Cardiovascular Society Antiplatelet Therapy Guidelines apps, pocket guides, slide decks and e-learning: http://www.ccsguidelineprograms.ca/index.php?option=com_content&view=article&id=141&Itemid=82
- Thrombosis Canada clinical guides: http://thrombosiscanada.ca/?page_id=18
- CHEST Antithrombotic Guidelines: http://www.chestnet.org/Guidelines-and-Resources/Guidelines-and-Consensus-Statements/Antithrombotic-Guidelines-9th-Ed
- HSF Stroke Assessment Pocket Cards http://www.strokebestpractices.ca/wp-content/uploads/2017/07/002-17_CSBP_StrokeAssessPocketGuide_7.5x4.25_EN_v6_LR.pdf
- Canadian Cardiovascular Society Atrial Fibrillation Guidelines 2016: http://www.onlinecjc.ca/article/S0828-282X(16)30829-7/fulltext
- Heart and Stroke Foundation Position Statement "Access to Medicine, Heart Disease and Stroke": http://www.heartandstroke.ca/-/media/pdf-files/canada/2017-position-statements/accessto-medicine-ps-eng.ashx?la=en&hash=F9A97F0D9E2A708E3AC20F2EAFA6631C2510605A

Patient Information

- Antiplatelets: http://www.heartandstroke.com/site/c.ikIQLcMWJtE/b.3484139/k.C87F/Heart_disease__Antiplatelets.htm
- Thrombosis Interest Group of Canada 'Medical Information for Patients taking Antiplatelets PDF: http://www.tigc.org/getattachment/ddd6fce2-ebc9-4ac5-b0ea-fae1b2fb5131/medical-information-for-patients-taking-antiplatel.aspx
- "Your Stroke Journey": http://www.strokebestpractices.ca/wp-content/uploads/2015/03/YOURSTROKEJOURNEY.FINAL_.ENGLISH..pdf
- Post-Stroke Checklist: http://www.strokebestpractices.ca/wp-content/uploads/2014/06/HSF%20Post%20Stroke%20Checklist_WEB.pdf

Summary of the Evidence 2018f

Aspirin therapy, provided acutely following ischemic stroke, is known to reduce the risk of recurrent (ischemic) stroke. In an updated Cochrane review, Sandercock et al. (2014) identified 8 RCTs (n=41,483 patients) that compared a single oral antiplatelet agent (aspirin, n=3 or ticlopidine, n=2) or a combination of antiplatelet agents (aspirin + dipyridamole and/or heparin, n=2) with control (placebo or no treatment). In 8/10 trials, therapy was initiated within one week following stroke. The dose of aspirin ranged from 160-325 mg/day and treatment duration ranged from 5 days to 3 months following stroke. Two large trials testing aspirin, started within 48 hours of stroke onset, contributed 98% of the data (CAST 1997, IST 1997). Antiplatelet therapy was associated with a significant reduction in the odds of being dead or dependent at final follow-up (OR= 0.95, 95% CI 0.91 to 0.99, p= 0.01). Treatment was also associated with a marginally significant reduction in death during treatment (OR= 0.92, 95% CI 0.85

to 1.00, p=0.05 and a significant reduction in the odds of death at a final follow-up (OR=0.92, 95% CI 0.87 to 0.99, p=0.01). Although antiplatelet therapy was associated with a significant increase in the odds of intracerebral hemorrhage (OR=1.23, 95% CI 1.00 to 1.50, p=0.04), a net reduction was reported in the odds of any stroke recurrence (i.e., ischemic or hemorrhagic; OR=0.88, 95% CI 0.80 to 0.97). For every 1,000 people treated with aspirin, 13 fewer people would avoid death or dependency, 9 fewer would avoid death and 7 fewer would avoid a recurrent stroke. The results from a patient-level meta-analysis using 3 RCTs, (Rothwell et al. 2016) suggest that the greatest reduction in early stroke recurrence associated with aspirin monotherapy is among patients presenting with mild or moderately disabling stroke. Aspirin therapy was not associated with a significant reduction in stroke recurrence among those with a severe stroke.

There is some evidence to suggest that dual antiplatelet therapy, provided in the early post-stroke period may help to reduce the risk of recurrent stroke. Greengage et al. (2012) included the results from 12 trials assessing various combinations and doses of other antiplatelet agents, in addition to aspirin. Based on the results from all trials, dual therapy was associated with significantly reduced risks of recurrent stroke (RR=0.67, 95% CI 0.49-0.93, p=0.02), composite of stroke, MI and vascular death (RR= 0.75; 95% CI, 0.56 – 0.99, p=0.04), without significant increases in ICH or major bleeding events. In contrast, the results of the TARDIS trial (Bath et al. 2017) suggest that triple antiplatelet therapy with aspirin, dipyridamole and clopidogrel, does not significantly reduce the risk of recurrent stroke, but does increase the risk of bleeding events.

Clopidogrel is indicated for acute management of ischemic stroke in patients who are not tolerant of aspirin. Two major trials, published within the previous 5 years, both with short-term outcomes, were positive. The most recent one, the Platelet-Oriented Inhibition in New TIA & Minor Ischemic Stroke (POINT) Trial (Johnston et al. 2018), enrolled 4,881 patients with recent (within previous 12 hours) minor stroke or TIA from centres located mainly in the United States. Patients were randomized to receive 81 mg aspirin + 75 mg clopidogrel or aspirin + placebo, for 90 days. The risk of ischemic stroke was significantly lower in the clopidogrel group (4.6% vs. 6.3%; HR=0.72, 95% CI 0.56–0.92, p= 0.01), although the risk of major hemorrhage was significantly increased (0.9% vs. 0.4%, HR=2.32, 95% CI 1.10–4.87, p= 0.02). The authors estimated that for every 1,000 patients treated with clopidogrel plus aspirin for 90 days, 15 ischemic strokes would be prevented but 5 major hemorrhages would result. Another positive trial was the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial, in which investigators randomized 5,170 patients from China with recent minor ischemic stroke (within previous 24 hours) or high-risk TIA to receive clopidogrel (75 mg/day) plus low-dose ASA (75 mg/day) or clopidogrel placebo plus aspirin for 90 days (Wang et al. 2013). Significantly fewer patients in the clopidogrel + aspirin group experienced a stroke within 90 days (Any stroke: 8.2% vs. 11.7%, HR=0.68, 95% CI 0.0.57-0.81, p<0.001) or an MI, stroke or vascular death stroke (8.4% vs. 11.9%, HR=0.69, 95% CI 0.58- 0.82, p<0.001). There was no difference in (any) bleeding events between groups (2.3% vs. 1.6%, p=0.09). In the Fast Assessment of Stroke and TIA to prevent Stroke Recurrence (FASTER) trial (Kennedy et al. 2007), randomized 392 patients presenting with minor stroke or TIA to receive clopidogrel or placebo and simvastatin or placebo within 24 hours of the qualifying event. In the antiplatelet arm of the trial, there were non-significant reductions in the risks of recurrent stroke (7.1% vs. 10.8%, RR=0.7, 95% CI 0.3-1.2, p=0.19) and the composite secondary outcome, which included myocardial infarction and death, associated with clopidogrel use. Clopidogrel use was associated with a significant 3% increase in risk (p=0.03) for symptomatic bleeding events.

The addition of dipyridamole to both aspirin and clopidogrel (i.e., triple antiplatelet therapy) to prevent recurrent events within 90 days was found to be associated with increased bleeding events in the TRADIS trial (Bath et al. 2018), compared with standard antiplatelet therapy using one or two agents. There was no significant difference between groups in the incidence or severity of stroke or TIA. The trial was stopped prematurely due to futility and safety concerns.

After thrombolysis, a portion of patients may develop reocclusion, which has been attributed to increased platelet aggregation. Therefore, antiplatelet therapy early after alteplase was thought to potentially reduce the risk of reocclusion and thereby improve functional outcome. However, the results from The Antiplatelet Therapy in Combination with rt-PA Thrombolysis in Ischemic Stroke (ARTIS) Trial suggest that treatment may be associated with harm. Zinkstok & Roos (2012) randomized 640 patients to receive 300 mg of aspirin intravenously within 90 minutes of alteplase treatment or standard treatment

(no aspirin). At the three-month follow-up, although there was no difference between groups in the odds of a good outcome, defined as mRS score of 0-2 (54% vs. 57.2%, OR=0.91, 95% CI 0.66 to 1.26), the risk of symptomatic ICH was significantly higher among patients in the early aspirin group (RR=2.78, 95% CI 1.01 to 7.63, p=0.04).

Controversy exists regarding the use of antiplatelets in the hyperacute management of pediatric patients following stroke. The Royal College of Physicians and the American Heart Association pediatric stroke guidelines both recommend the use of aspirin unless there is a known dissection or cardiac clot, in which case low molecular weight heparin is recommend (Paediatric Stroke Working Group, 2004; Roach et al. 2008). Conversely, the American College of Chest Physicians guidelines (Monagle et al. 2012) suggests supportive care over anticoagulation or aspirin therapy in the absence of a documented, ongoing cardioembolic source. For neonates with a first ischemic stroke with a documented cardioembolic source, anticoagulation with UFH or LMWH is recommended.

Reference List and Evidence Tables

Evidence Table 6 and References available on website at www.strokebestpractices.ca

Section Seven: Early Management of Patients Considered for Hemicraniectomy (Sixth Edition, 2018)

7. Early Management of Patients Considered for Hemicraniectomy Recommendations

7.0 Hemicraniectomy should be considered in patients in the early stages of extensive (malignant) middle cerebral artery territory ischemic stroke as a life-saving measure for patients willing to accept a significant risk of living with a degree of disability that may leave them dependent on others for their activities of daily living [Evidence Level A for patients age 18 – 60 years; Evidence Level B for patients 60 – 80 years].

7.1 Patient Selection

i. Patients who meet the following criteria alone or in combination should be considered for hemicraniectomy [Evidence Level A]:

   a. Patients over the age of 18;

   b. Children under 18 years with progressive extensive (malignant) MCA syndrome [Evidence Level C];

   c. Malignant middle cerebral artery (MCA) infarct with evidence of significant edema and mass effect;

   d. Infarction size greater than 50% MCA territory on visual inspection, or an ischemic lesion volume greater than 150 cm^3;

ii. Posterior fossa decompression can be considered in selected patients with significant cerebellar stroke with evidence of mass effect and / or hydrocephalus [Evidence Level C].

iii. If a potential patient's location is initially outside a comprehensive stroke centre, the patient should have expedited transfer to a tertiary or quaternary centre where advanced stroke care and neurosurgical services are available [Evidence Level C].

7.2 Initial Clinical Evaluation

i. Urgent consultation with a stroke specialist for assessment and for determination to involve neurosurgery [Evidence Level C].

ii. For patients who meet criteria for potential hemicraniectomy during initial assessment, an urgent neurosurgical consultation should be initiated, either in-person, by telephone or using telemedicine (Telestroke services) [Evidence Level C].

iii. Initiate a discussion with patient, family members and legal decision-maker regarding a potential hemicraniectomy [Evidence Level C].

   a. Key issues to be discussed with the patient and/or alternate decision-makers include: stroke diagnosis and prognosis if untreated, the risks of surgery, the possible and likely outcomes following surgery including the odds of living with severe disability, and the patient's previously expressed wishes concerning treatment in the event of catastrophic illness and probability of living with severe handicap.

   b. The discussion with the patient and decision-makers should state more clearly that there is a survival benefit, but an uncertain impact on quality of life and disability. Furthermore that even with treatment, a good outcome (MRS 0-2) is rare.

7.3 Patient Management Prior to Hemicraniectomy Surgery

i. In patients selected for decompressive hemicraniectomy, proceed urgently to surgery prior to significant decline in GCS or pupillary change [Evidence Level C]. Proceeding within 48 hours from stroke onset may provide benefit [Evidence Level B].

ii. Patients should be transferred to an intensive care unit or neuro step-down unit for close and frequent monitoring of neurological status prior to surgery [Evidence Level C].

   a. Monitoring should include assessments of level of consciousness (e.g., Canadian Neurological Scale Score), worsening symptom severity, and blood pressure at least hourly; more frequently as the individual patient condition requires [Evidence Level C].

   b. If changes in status occur, the stroke team and neurosurgeon should be notified immediately for re-evaluation of the patient [Evidence Level C]. Change in status may include level of drowsiness/consciousness, change in CNS score by greater than or equal to 1 point, or change in NIHSS score by greater than or equal to 4 points.

   c. Repeat CT scans are recommended for patients when deterioration in neurological status occurs [Evidence Level C].

iii. Patients with suspected elevation in intracranial pressure may be managed according to institutional protocols (e.g, administration of hyperosmolar therapy, head of bed elevation) [Evidence Level C].

Rationale

The morbidity and mortality for the routine care of patients with malignant hemispheric strokes is higher than other stroke subgroups, and there is evidence to support that, in selected cases, hemicraniectomy may significantly reduce mortality but it could leave people with significant disability and possible dependence for activities of daily living. Consideration for hemicraniectomy must be individualized; there is a strong need for careful clinical consideration and patient selection. Decisions regarding hemicraniectomy involve several members of the multidisciplinary stroke team, including neurology, neurosurgery, intensive care and nursing through a collaborative and coordinated system of care.

System Implications

1. Timely access to diagnostic services such as neuro-imaging, with protocols for prioritizing potential stroke patients.
2. Timely access to specialized stroke care (i.e. a neuro-intensive care unit) and neurosurgical specialists for consultation and patient management, including rapid referral process if neurosurgical services not available within the initial treating hospital.
3. Access to organized stroke care, ideally stroke units with a critical mass of trained staff and an interdisciplinary stroke team.
4. Education for Emergency Department, and hospital staff on the characteristics and urgency for management of severe stroke patients.

Performance Measures

1. Risk-adjusted mortality rates for severe stroke patients who undergo hemicraniectomy (in-hospital, 30-day and one year) (core).

2. Percentage of hemicraniectomy patients who experience intraoperative complications and/or mortality during surgery or within first 24 hours post-operatively.
3. Distribution of functional ability measured by standardized functional outcome tools at time of discharge from hospital and over time in the community (e.g., 90 days, 1 year).

Measurement Notes:

a. Mortality rates should be risk-adjusted for age, gender, stroke severity and comorbidities

b. Time interval measurements should start from symptom onset of known or from triage time in the Emergency Department as appropriate.

Implementation Resources and Knowledge Transfer Tools

Health Care Provider Information

- Canadian Stroke Best Practices Appendix Three: Screening and Assessment Tools for Acute Stroke Severity
- Canadian Stroke Best Practices Table 2B: Recommended Laboratory Investigations for Acute Stroke and Transient Ischemic Attack
- HSF Stroke Assessment Pocket Cards http://www.strokebestpractices.ca/wp-content/uploads/2017/07/002-17_CSBP_StrokeAssessPocketGuide_7.5x4.25_EN_v6_LR.pdf

Patient Information

- "Your Stroke Journey": http://www.strokebestpractices.ca/wp-content/uploads/2015/03/YOURSTROKEJOURNEY.FINAL_.ENGLISH.pdf
- Post-Stroke Checklist: http://www.strokebestpractices.ca/wp-content/uploads/2014/06/HSF%20Post%20Stroke%20Checklist_WEB.pdf

Summary of the Evidence 2018

The benefit of decompressive hemicraniectomy (versus standard medical treatment) early following malignant middle cerebral artery (MCA) infarction in patients <60 years has been evaluated in three major RCTs, all of which had comparable inclusion criteria and primary outcome measures (DESTINY 1, HAMLET and DECIMAL). In the first DESTINY trial (Juttler et al. 2007), which randomized 32 patients to receive either surgical plus medical treatment or to conservative medical treatment only, there was a trend towards more favourable outcome (mRS 0-3) among patients in the surgical arm at 6 months (47% vs. 27%, (p=0.23; OR=2.44, 95% CI 0.55 to 10.83). Thirty-day survival was significantly higher among patients in the surgical arm (88% vs. 47%, OR=6.4, 95% CI 1.35 to 29.2). In the HAMLET trial (Hofmeijer et al. 2009), while there were no differences between groups in the proportion of patients who had experienced either a good (mRS 0-1) or poor (mRS 4-6) outcome at 1 year, surgery was associated with a 38% absolute risk reduction (95% CI 15 to 60, p=0.002) in 1-year mortality. Patients who received decompressive hemicraniectomy had significantly lower mean physical summary scores on the SF-36 Quality of Life scale, compared with those treated with medical care only (29 vs. 36; mean difference = −8, 95% CI -14 to -1, p = 0.02). No significant differences were found between the two treatment groups with respect to the mental summary score of the SF-36 score, mood, or the proportion of patients or carers dissatisfied with treatment. At 3 years follow-up, a significantly lower percentage of patients in the surgical group had died (26% vs. 63%, p=0.002) (Geurts et al. 2013). In the DECIMAL trial (Vahedi et al. 2007b), while there was no difference in the number of patients with mRS scores of 0-3 between groups at 6 months, a significantly higher proportion of surgical patients had mRS scores of 0-4 and there was

also a survival advantage among patients in the surgical arm. The results from all three trials were pooled in a recent Cochrane review (Cruz-Flores et al. 2012), which reported that decompressive hemicraniectomy was associated with a significantly reduced risk of death at the end of follow-up (OR = 0.19, 95% CI 0.09 to 0.37) and the risk of death or severe disability (mRS > 4) at 12 months (OR = 0.26, 95% CI 0.13 to 0.51). Surgery was also associated with a non-significant trend towards increased survival with severe disability (mRS of 4 or 5; OR = 2.45, 95% CI 0.92 to 6.55). No significance between group differences were found for the combined outcome death or moderate disability (mRS 4-6) at the end of follow-up (OR = 0.56, 95% CI 0.27 to 1.15). In a more recent systematic review, which included the results from 7 trials, (Qureshi et al. 2016), similar findings were reported. The odds of a favourable outcome (mRS 0-3) and survival at 6-12 months were significantly increased for patients in the hemicraniectomy group (OR=2.04, 95% CI 1.03-4.02, p=0.04 and OR=5.56, 95% CI 3.40-9.08, p<0.001, respectively).

The upper age limit for decompressive hemicraniectomy in malignant MCA infarct has been a focus of debate, given that the evidence is conflicting. Using data from 276 patients, obtained from 17 case series McKenna et al. (2012) reported that patients 60 years of age and older who underwent surgery had a higher mortality rate and poorer outcome compared with younger patients. In the DECIMAL trial's surgical group, younger age correlated with better outcomes at 6 months ($r = 0.64$, $p < 0.01$) (Vahedi et al., 2007b). A recent retrospective study investigating decompressive hemicraniectomy in older adults compared the outcomes of individuals aged between 61-70 years and those > 70 years of age (Inamasu et al. 2013). The mortality rate was significantly higher among those in the older cohort (60% vs. 0%, $p = 0.01$). However, there is also evidence suggesting that older patients also benefit from surgery. Zhao et al (2012) randomized 47 patients, aged 18-80 years, 29 of whom were >60-80 years. Decompressive hemicraniectomy within 48 hours of stroke onset was associated with a significant overall reduction in mortality at both 6 (12.5% vs. 60.9 %, $p = 0.001$) and 12-month follow-up (16.7% vs. 69.6 %, $p < 0.001$). In the subgroup of older patients, significantly fewer patients in the surgical arm had an unfavourbale outcome (mRS 5–6) at 6 months (31.2% vs. 92.3%, ARR=61.1%; 95 % CI 34.1 to 88.0) with similar results reported at one year (ARR = 62.5%; 95% CI 38.8 to 86). Authors from the HAMLET trial reported that there was a trend towards greater benefit of surgery in patients between the ages of 51–60 compared with patients 50 years of age or younger (Hofmeijer et al. 2009). Most recently, in the DESTINY II trial (Juttler et al. 2014), 112 patients ≥61 years admitted with unilateral MCA infarction were randomized to receive conservative treatment or early surgical intervention. A significantly higher proportion of patients in the surgical group were alive and living without severe disability at 6 months (38% vs.18%, OR=2.91, 95% CI 1.06-7.49, p=0.04). Although no patients in either the surgical or medical care groups had good outcome (mRS score of 0-2) at 6 or 12 months, a significantly higher percentage of patients in the surgical group had mRS scores of 3-4 (38% vs. 16%) and a significantly lower percentage had mRS scores of 5-6 (62% vs. 84%).

Timing of surgical intervention is also an important consideration when deciding whether to perform decompressive hemicraniectomy. In the HAMLET trial there was a significant reduction in both mortality and poor outcome when patients were randomized to surgery within 48 hours of stroke onset, with no significant benefit when patients received surgery within 96 hours (Hofmeijer et al., 2009). However, in pooled analysis using the sub group results from the DECIMAL, DESTNY I and HAMLET trials examining the outcomes of patients treated within 24 hours vs. >24 hours following stroke onset, no differences in outcome were reported (Vahedi et al., 2007a). Taken together, these findings suggest that the appropriate time interval to perform decompressive hemicraniectomy may be within 48 hours, further research is needed to determine if earlier treatment (e.g., with 24 hours) is associated with superior outcomes.

There is insufficient evidence to recommend the use of corticosteroids to reduce cerebral edema and intracranial pressure following acute ischemic stroke. The results from a Cochrane review (Sandercock & Sloane 2011) included the results from 8 RCTs (466 participants). Pooling of data was only possible for the outcome of death. The use of corticosteroids (versus) placebo was not associated with a reduced risk of death at one month (OR=0.97, 95% CI 0.63-1.47, p=0.87) or one year after stroke (OR=0.87, 95% CI 0.57-1.34, p=0.53).

Reference List and Evidence Tables

Evidence Table 7 and References available on website at www.strokebestpractices.ca

CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS, SIXTH EDITION

PART THREE: ACUTE INPATIENT STROKE CARE RECOMMENDATIONS

Section 8: Acute Stroke Unit Care (Sixth Edition, 2018)

8. Acute Stroke Unit Care Recommendations

8.1 Patients admitted to hospital with an acute stroke or transient ischemic attack should be treated on an inpatient stroke unit [Evidence Level A] as soon as possible; ideally within 24 hours of hospital arrival [Evidence Level C].

i. Patients should be admitted to a stroke unit which is a specialized, geographically defined hospital unit dedicated to the management of stroke patients [Evidence Level A].

   a. For facilities without a dedicated stroke unit, the facility must strive to focus care on the priority elements identified for comprehensive stroke care delivery (including clustering patients, interdisciplinary team, access to early rehabilitation, stroke care protocols, case rounds, patient education). *Refer to Box 8A: Optimal Acute Stroke Care for further information.*

ii. The core interdisciplinary team on the stroke unit should consist of health care professionals with stroke expertise including physicians, nurses, occupational therapists, physiotherapists, speech-language pathologists, social workers, and clinical nutritionists (dietitians) [Evidence Level A].

   a. All stroke teams should include hospital pharmacists to promote patient safety, medication reconciliation, provide education to the team and patients/family regarding medication(s) (especially side effects, adverse effects, interactions), discussions regarding adherence, and discharge planning (such as special needs for patients, e.g., individual dosing packages) [Evidence Level B].

   b. Additional members of the interdisciplinary team may include discharge planners or case managers, (neuro) psychologists, palliative care specialists, recreation and vocational therapists, spiritual care providers, peer supporters and stroke recovery group liaisons [Evidence Level B].

iii. The interdisciplinary team should assess patients within 48 hours of admission to hospital and formulate a management plan [Evidence Level B].

   a. Clinicians should use standardized, valid assessment tools to evaluate the patient's stroke-related impairments and functional status [Evidence Level B].

   b. Assessment components should include dysphagia, mood and cognition, mobility, functional assessment, temperature, nutrition, bowel and bladder function, skin breakdown, discharge planning, prevention therapies, venous thromboembolism prophylaxis [Evidence Level B]. *Refer to Section 9 of this module for further information.*

   c. Alongside the initial and ongoing clinical assessments regarding functional status, a formal and individualized assessment to determine the type of ongoing post-acute rehabilitation services required should occur as soon as the status of the patient has stabilized, and within the first 72 hours post-stroke, using a standardized protocol (including tools such as the alpha-FIM) [Evidence Level B]. *Refer to Canadian Stroke Best Practice Recommendations Stroke Rehabilitation Module section 3 for further*

information.

iv. Any child admitted to hospital with stroke should be managed in a centre with pediatric stroke expertise when available; if there is no access to specialized pediatric services, children with stroke should be managed using standardized pediatric stroke protocols [Evidence Level B].

8.2 **Management of Stroke that Occurs While Patient Already in Hospital:**

i. Hospital in-patients who experience a new stroke while hospitalized should undergo immediate assessment by a physician with stroke expertise, undergo neurovascular imaging without delay, and be assessed for eligibility for intravenous alteplase and/or endovascular thrombectomy [Evidence Level B]. *Refer to sections 4 and 5 for additional information.*

a. All hospitals should have protocols in place for management of acute inpatient stroke and all staff trained on these protocols, especially in units with higher risk patients [Evidence Level C].

BOX 8A: OPTIMAL ACUTE INPATIENT STROKE CARE

DEFINTION:

A stroke unit is *a specialized, geographically defined hospital unit dedicated to the management of stroke patients and staffed by an experienced interdisciplinary stroke team. Refer to the resource Taking Action Towards Optimal Stroke Care for detailed information about stroke unit criteria.*

Alternate Stroke Care Models: *It is recognized that many models of acute stroke care exist across Canada. Many organizations do not have the official administrative designation as an 'acute stroke unit'; however they have most or all of the stroke unit criteria in place and should be recognized as attempting to meet optimal stroke care in the face of administrative/structural resource challenges. These models are sometimes referred to as clustered acute stroke care, or purposeful grouping of stroke patients.*

Core Elements of Comprehensive Stroke and Neurovascular Care (Based on Stroke Unit Trialists Collaboration 2007)

a. It is recognized that not all hospitals are able to deliver all of the stroke unit elements, and every hospital should be ***Taking Action*** to establish protocols and processes of care to implement as many elements as possible to achieve optimal stroke care delivery within their geographic location, hospital volumes and resource availability (human, equipment, funding). *Refer to Taking Action Towards Optimal Stroke Care resource kit at www.strokebestpractices.ca*

b. Specialized care for patients with ischemic stroke, intracerebral hemorrhage (ICH), and transient ischemic attack (TIA) (care may be expanded in some institutions to include patients with subarachnoid hemorrhage [SAH] and other neurovascular conditions);

c. Dedicated stroke team with broad expertise – including neurology, nursing, neurosurgery, physiatry, rehabilitation professionals, pharmacists, and others;

d. Consistent clustered model where all stroke patients are cared for on the same hospital ward with dedicated stroke beds by trained and experienced staff, including rehabilitation professionals;

e. Access to 24/7 imaging and interventional neuroradiology expertise;

f. Emergent neurovascular surgery access;

g. Protocols in place for hyperacute and acute stroke management, and seamless transitions

between stages of care (including pre-hospital, Emergency Department and inpatient care);

h. Dysphagia screening protocols in place to assess all stroke patients without prolonged time delays prior to commencing oral nutrition and oral medications;

i. Access to post-acute rehabilitation services, including inpatient, community-based, and/or early supported discharge (ESD) therapy;

j. Discharge planning starting as soon as possible after admission, and anticipating discharge needs to facilitate smooth transitions;

k. Daily/bi-weekly patient care rounds with interdisciplinary stroke team to conduct case reviews, discuss patient management issues, family concerns or needs, and discharge planning (discharge or transition to the next step in their care, timing, transition requirements);

l. Patient and family education that is formal, coordinated, and addresses learning needs and responds to patient and family readiness;

m. Provision of palliative care when required, ideally by a specialized palliative care team;

n. Ongoing professional development for all staff – stroke knowledge, evidence-based best practices, skill building, orientation of trainees;

o. Involvement in clinical research for stroke care.

Rationale

Stroke unit care reduces the likelihood of death and disability by as much as 30 percent for men and women of any age with mild, moderate, or severe stroke. Stroke unit care is characterized by a coordinated interdisciplinary team approach for preventing stroke complications, preventing stroke recurrence, accelerating mobilization, and providing early rehabilitation therapy. Evidence suggests that stroke patients treated on acute stroke units have fewer complications, earlier mobilization, and pneumonia is recognized earlier. Patients should be treated in a geographically defined unit, as care through stroke pathways and by roving stroke teams do not provide the same benefit as stroke units. Access to early rehabilitation is a key aspect of stroke unit care. For patients with stroke, rehabilitation should start as early as possible and rehabilitation should be considered an intervention that can occur in any and all settings across the continuum of stroke care.

System Implications

1. Organized systems of stroke care including stroke units with a critical mass of trained staff (interdisciplinary team). If not feasible, then mechanisms for coordinating the care of stroke patients to ensure use of best practices and optimal outcomes.
2. Protocols and mechanisms to enable the rapid transfer of stroke patients from the Emergency Department to a specialized stroke unit as soon as possible after arrival in hospital, ideally within the first six hours.
3. Comprehensive and advanced stroke care centres should have leadership roles within their geographic regions to ensure specialized stroke care access is available to patients who may first appear at general health care facilities (usually remote or rural centres) and facilities with basic stroke services only.
4. Telestroke service infrastructure and utilization should be optimized to ensure access to specialized stroke care across the continuum to meet individual needs (including access to rehabilitation and stroke specialists) including the needs of northern, rural and remote residents in Canada.

5. Information on geographic location of stroke units and other specialized stroke care models available to community service providers, to facilitate navigation to appropriate resources and to strengthen relationships between each sector along the stroke continuum of care.

Performance Measures

1. **Number of stroke patients who are admitted to hospital and treated on a specialized stroke unit at any time during their inpatient hospital stay for an acute stroke event (numerator) as a percentage of total number of stroke patients admitted to hospital (core).**
2. **Percentage of patients discharged to their home or place of residence following an inpatient admission for stroke (core).**
3. **Proportion of stroke patients who die in hospital within 7 days and within 30 days of hospital admission for an index stroke (reported by stroke type) (core).**
4. Proportion of total time in hospital for an acute stroke event spent on a stroke unit.
5. Proportion of patients admitted to a stroke unit, who arrive in the stroke unit within 24 hours of Emergency Department arrival.
6. Proportion of designated stroke unit beds that are filled with stroke patients (weekly average).
7. Percentage increase in telehealth or telestroke coverage to remote communities to support organized stroke care across the continuum.

Refer to Canadian Stroke Quality and Performance Measurement Manual for detailed indicator definitions and calculation formulas. www.strokebestpractices.ca/

Measurement Notes

a. Performance measure 1: calculate for all cases, and then stratify by type of stroke.

b. Definition of stroke unit varies widely from institution to institution. Where stroke units do not meet the criteria defined in the recommendation, then a hierarchy of other stroke care models could be considered: a) dedicated stroke unit; (b) designated area within a general nursing unit or neuro-unit where stroke patients are clustered; (c) mobile stroke team care; (d) managed on a general nursing unit by staff using stroke guidelines and protocols.

c. Institutions collecting this data must note their operational definition of “stroke unit” to ensure standardization and validity when data is reported across institutions.

d. Performance measure 5 – start time for assessing stroke unit admission within 24 hours should be Emergency Department triage time.

e. Patient and family experience surveys should be in place to monitor care quality during inpatient stroke admissions

Implementation Resources and Knowledge Transfer Tools

Health Care Provider Information

- Canadian Stroke Best Practice Recommendations Acute Stroke Management Module: Table 2A: Recurrent Stroke Risk Levels and Initial Management
- Canadian Stroke Best Practice Recommendations PreHospital and Emergency Department

Module: Table 2B: Recommended Laboratory Investigations for Patients with Acute Stroke or Transient Ischemic Attack
- Canadian Stroke Best Practice Recommendations Acute Stroke Management Module: Appendix Three Screening and Assessment Tools for Acute Stroke Severity
- HSF Stroke Assessment Pocket Cards: http://www.strokebestpractices.ca/wp-content/uploads/2017/07/002-17_CSBP_StrokeAssessPocketGuide_7.5x4.25_EN_v6_LR.pdf

Patient Information

- "Your Stroke Journey": http://www.strokebestpractices.ca/wp-content/uploads/2015/03/YOURSTROKEJOURNEY.FINAL_.ENGLISH..pdf
- Post-stroke Checklist: http://www.strokebestpractices.ca/wp-content/uploads/2014/06/HSF%20Post%20Stroke%20Checklist_WEB.pdf

Summary of the Evidence 2018

It is now well-established that patients who receive stroke unit care are more likely to survive, return home, and regain independence compared to patients who receive less organized forms of care. Stroke unit care is characterized by an experienced interdisciplinary stroke team, including physicians, nurses, physiotherapists, occupational therapists, speech therapists, among others, dedicated to the management of stroke patients, often located within a geographically defined space. Other features of stroke units include staff members who have an interest in stroke, routine team meetings, continuing education/training, and involvement of caregivers in the rehabilitation process. In an updated Cochrane Review, the Stroke Unit Trialists' Collaboration (2013) identified 28 randomized and quasi-randomized trials (n=5,855) comparing stroke unit care with alternative, less organized care (e.g., an acute medical ward). Compared to less organized forms of care, stroke unit care was associated with a significant reduction in the odds of death (OR= 0.81, 95% CI 0.69 to 0.94, p = 0.005), death or institutionalization (OR=0.78, 95% CI 0.68 to 0.89, p = 0.0003), and death or dependency (OR= 0.79, 95% CI 0.68 to 0.90, p = 0.0007) at a median follow-up period of one year. Based on the results from a small number of trials, the authors also reported that the benefits of stroke unit care are maintained for periods up to 5 and 10 years post stroke. Moreover, subgroup analyses demonstrated benefits of stroke unit care regardless of sex, age, or stroke severity. Saposnik et al. (2011) investigated the differential impact of stroke unit care on four subtypes of ischemic stroke (cardioembolic, large artery disease, small vessel disease, or other) and reported that stroke unit care was associated with reduced 30-day mortality across all subtypes.

To determine if the benefits of stroke unit care demonstrated in clinical trials can be replicated in routine clinical practice, Seenan et al. (2007) conducted a systematic review of 25 observational studies (n=42,236) comparing stroke unit care to non-stroke unit care. Stroke unit care was associated with a reduction in the risk of death (OR=0.79, 95% CI 0.73 to 0.86, p<0.001) and of death or poor outcome (OR=0.87, 95% CI=0.80 to 0.95; p=0.002) within one-year of stroke. Similar findings were reported for the outcome of death at one year in a secondary analysis limited to multi-centered trials (OR=0.82, 95% CI 0.77 to 0.87, p<0.001).

In-hospital Stroke

Estimates of persons who experience a stroke while already hospitalized for other conditions range from 4% to 17% (as cited by Cumbler et al. 2014). Many of these patients have pre-existing stroke risk including hypertension, diabetes, cardiac diseases, and dyslipidemia (Vera et al. 2011). These in-

hospital strokes often occur following cardiac and orthopedic procedures, usually within 7 days of surgery. There is evidence to suggest that, compared with persons who suffer a stroke in the community, patients who experience an in-hospital stroke have more severe strokes, worse outcomes and do not receive care in as timely a fashion. Of 15,815 consecutive patients included in the J-MUSIC registry, (Kimura et al 2006), 694 (4.4%) experienced an in-hospital ischemic stroke. The mean admission NIHSS score was significantly higher for patients with in-hospital stroke (14.6 vs. 8.1, p<0.0001). In-hospital stroke was an independent predictor of severe stroke, defined as NIHSS score ≥11 (OR=3.27, 95% CI 2.7-3.88, p<0.0001). Significantly more in-hospital stroke patients died both in hospital (19.2% vs. 6.8%, p<0.0001) and within 28 days (12.1% vs. 4.8%, p<0.0001). Farooq et al. (2008) compared the outcomes of 177 patients who experienced an in-hospital stroke and 2,566 who were admitted from the community to 15 hospitals in a single state over a 6-month period. In-hospital case fatality was significantly higher among in-hospital patients (14.6% vs. 6.9%, p=0.04). The distribution of mRS scores was shifter towards poorer outcomes for the in-hospital group (p<0.001) and fewer in-hospital stroke patients were discharged home (22.9% vs. 52.2%, p<0.01).

One of the largest studies to examine quality of care received and stroke outcome included 21,349 patients who experienced an in-hospital ischemic stroke and were admitted to 1,280 hospitals participating in the Get with the Guideline Stroke registry from 2006-2012, and 928,885 patients admitted to hospitals from the community during the same time frame (Cumbler et al. 2014). In-hospital stroke patients were significantly less likely to meet 7 achievement standards (t-PA within 3 hours, early antithrombotics, DVT prophylaxis, antithrombotics/anticoagulants on discharge, statin meds), and were less likely to receive a dysphagia screen or receive t-PA within 3.5-4.5 hours, but were more likely to receive a referral for rehabilitation and to receive intensive statin therapy. When quality/achievement measures were combined, in-hospital stroke patients were less likely to receive investigations/care for which they were eligible (82.6% vs. 92.8%, p<0.0001). In-hospital stroke patients also experienced worse outcomes. They were less likely to be independent in ambulation at discharge (adj OR=0.42, 95% CI 0.39-0.45, p<0.001), to be discharged home (adj OR=0.37, 95% CI 0.35-0.39, p<0.001) and the odds of in-hospital mortality were significantly higher (adj OR=2.72, 95% CI 2.57-2.88, p<0.001). Although a higher percentage of patients with in-hospital stroke received thrombolytic therapy with t-PA (11% vs. 6.6%), fewer received the treatment within 3-hours (31.6% vs. 73.4%, p<0.0001).

Reference List and Evidence Tables

Evidence Table 1 and References available on website at www.strokebestpractices.ca

Section 9: Inpatient Prevention and Management of Complications following Stroke (Sixth Edition, 2018)

9. Inpatient Prevention and Management of Complications Recommendations

9.0 Appropriate **investigations and management strategies** should be implemented for all hospitalized stroke and TIA patients to optimize recovery, avoid complications, prevent stroke recurrence, and provide palliative care when required. (no changes for 2018)

i. During acute inpatient care, stroke patients should undergo appropriate investigations to determine stroke mechanism and guide stroke prevention and management decisions [Evidence Level B].

ii. Individualized care plans should address nutrition, oral care, mobilization and incontinence, and reduce the risk of complications such as urinary tract infection, aspiration pneumonia, and venous thromboembolism [Evidence Level B].

iii. Discharge planning should begin as a component of the initial admission assessment and continue throughout hospitalization as part of ongoing care of hospitalized acute stroke patients [Evidence Level B]. *Refer to Canadian Stroke Best Practice Recommendations Managing Stroke Transitions of Care Module section 3 for additional information*.

iv. All patients, family members and informal caregivers should receive timely and comprehensive information, education and skills training by all interdisciplinary team members [Evidence Level A]. *Refer to Canadian Stroke Best Practice Recommendations Managing Stroke Transitions of Care Module sections 1 and 2 for additional information.*

v. A past history of depression should be identified for all acute stroke inpatients [Evidence Level C]. *Refer Canadian Stroke Best Practice Recommendations Mood, Cognition and Fatigue Module section 1 for additional information.*

vi. Patients should undergo an initial screening for vascular cognitive impairment when indicated [Evidence Level B]. *Refer Canadian Stroke Best Practice Recommendations Mood, Cognition and Fatigue Module Section 2 for additional information.*

9.1 Cardiovascular Investigations

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

ii. Echocardiography, either 2-D or transesophageal, should be considered for patients with suspected embolic stroke and normal neurovascular imaging [Evidence Level B], as well as no contraindications for anticoagulant therapy. This is particularly relevant for younger adults with stroke or TIA and unknown etiology.

iii. Children with stroke should undergo a comprehensive cardiac evaluation including echocardiography, as well as detailed rhythm monitoring if clinically indicated [Evidence Level B].

9.2 Venous Thromboembolism Prophylaxis

i. All stroke patients should be assessed for their risk of developing venous thromboembolism (deep vein thrombosis and pulmonary embolism). ***Patients at high risk include those who are unable to move one or both lower limbs; those who are unable to mobilize independently; a previous history of venous thromboembolism; dehydration; and comorbidities such as***

cancer.

ii. Patients at high risk of venous thromboembolism should be started on thigh-high intermittent pneumatic compression devices (IPC) or pharmacological venous thromboembolism prophylaxis immediately if there is no contraindication (e.g. systemic or intracranial hemorrhage) [Evidence Level A]. At present, there is no direct evidence to suggest the superiority of one approach over the other.

a. If IPC is selected, it should be applied as soon as possible and within the first 24 hours after admission. IPC should be discontinued when the patient becomes independently mobile, at discharge from hospital, if the patient develops any adverse effects, or by 30 days (whichever comes first) [Evidence Level B].

1) For patients wearing IPC devices, skin integrity should be assessed daily [Evidence Level B].

2) Consultation with a wound care specialist is recommended if skin breakdown begins during IPC therapy [Evidence Level C].

3) If IPC is considered after the first 24 hours of admission, venous leg Doppler studies should be considered [Evidence Level C].

b. Low molecular weight heparin (i.e., enoxaparin) should be considered for patients with acute ischemic stroke at high risk of venous thromboembolism; or unfractionated heparin for patients with renal failure [Evidence Level A].

c. For stroke patients admitted to hospital and remaining immobile for longer than 30 days, the use of ongoing venous thromboembolism prophylaxis (e.g. with pharmacological venous thromboembolism prophylaxis) is recommended [Evidence Level C].

iii. The use of anti-embolism stockings alone for post-stroke venous thromboembolism prophylaxis is not recommended [Evidence Level A].

iv. Early mobilization and adequate hydration should be encouraged for all acute stroke patients to help prevent venous thromboembolism [Evidence Level C].

9.3 Temperature Management (no changes for 2018)

i. Temperature should be monitored as part of vital sign assessments; ideally every four hours for the first 48 hours, and then as per ward routine or based on clinical judgment [Evidence Level C].

ii. For temperature greater than 37.5 Celsius, increase frequency of monitoring, initiate temperature-reducing care measures, investigate possible infection such as pneumonia or urinary tract infection [Evidence Level C], and initiate antipyretic and antimicrobial therapy as required [Evidence Level B].

9.4 Mobilization (new changes for 2018)

Mobilization is defined as 'the process of getting a patient to move in the bed, sit up, stand, and eventually walk.'

4) All patients admitted to hospital with acute stroke should have an initial assessment, conducted by rehabilitation professionals, as soon as possible after admission [Evidence Level A].

5) Initial screening and assessment should be commenced within 48 hours of admission by rehabilitation professionals in direct contact with the patient [Evidence Level C]. *Refer to Canadian Stroke Best Practice Recommendations Stroke Rehabilitation module for additional recommendations on mobilization following an acute stroke*.

6) Rehabilitation therapy should begin as early as possible once the patient is determined to be medically able to participate in active rehabilitation [Evidence Level A].

7) Frequent, brief, out-of-bed activity involving active sitting, standing, and walking, beginning within 24 hours of stroke onset is recommended if there are no contraindications [Evidence Level B]. More intense early sessions are not of more benefit. Clinical judgment should be used.

Note: Contraindications to early mobilization include, but are not restricted to, patients who have had an arterial puncture for an interventional procedure, unstable medical conditions, low oxygen saturation, and/or lower limb fracture or injury.

9.5 Seizure Management

i. New-onset seizures in admitted patients with acute stroke should be treated using appropriate short-acting medications (e.g. lorazepam IV) if they are not self-limiting [Evidence Level C].

   a. A single, self-limiting seizure occurring at the onset, or within 24 hours after an ischemic stroke (considered an "immediate" post-stroke seizure) should not be treated with long-term anticonvulsant medications [Evidence Level C].

   b. Patients that have an immediate post-stroke seizure should be monitored for recurrent seizure activity during routine monitoring of vital signs and neurological status. Recurrent seizures in patients with ischemic stroke should be treated as per treatment recommendations for seizures in other neurological conditions [Evidence Level C].

ii. Seizures are a common presentation with stroke in neonates and children. Consider enhanced or increased seizure/electroencephalogram monitoring in at risk populations such as neonates, children with stroke and adults with otherwise unexplained reduced level of consciousness [Evidence Level B].

   a. Other investigations may include electroencephalogram (EEG) and tests to rule out other precipitating factors of seizures (e.g., infections) and may be warranted in acute stroke patients with seizures based on patient factors and clinical judgement [Evidence Level C].

   b. Prophylactic use of anticonvulsant medications in patients with ischemic stroke is not recommended [Evidence Level B] and there is some evidence to suggest possible harm with negative effects on neurological recovery [Evidence Level B].

9.6 Nutrition and Dysphagia (no changes for 2018)

i. Interdisciplinary team members should be trained to complete initial swallowing screening for all stroke patients to ensure patients are screened in a timely manner [Evidence Level C].

ii. The swallowing, nutritional and hydration status of stroke patients should be screened as early as possible, ideally on the day of admission, using validated screening tools [Evidence Level B*].*

iii. Abnormal results from the initial or ongoing swallowing screens should prompt referral to a speech-language pathologist, occupational therapist, and/or dietitian for more detailed assessment and management of swallowing, nutritional and hydration status [Evidence Level C]. An individualized management plan should be developed to address therapy for dysphagia, nutrition needs, and specialized nutrition plans [Evidence Level C].

iv. Stroke patients with suspected nutritional concerns, hydration deficits, dysphagia, or other comorbidities that may affect nutrition (such as diabetes) should be referred to a dietitian for recommendations:

   a. to meet nutrient and fluid needs orally while supporting alterations in food texture and fluid consistency recommended by a speech-language pathologist or other trained professional [Evidence Level B];

   b. for enteral nutrition support (nasogastric tube feeding) in patients who cannot safely swallow or meet their nutrient and fluid needs orally. The decision to proceed with tube feeding should be made as early as possible after admission, usually within the first

three days of admission in collaboration with the patient, family (or substitute decision maker), and interdisciplinary team [Evidence Level B]. *Refer to Canadian Stroke Best Practice Recommendations Stroke Rehabilitation module section 7 for additional information on dysphagia screening, assessment and management.*

9.7 Continence

i. The use of indwelling catheters should be used cautiously due to the risk of urinary tract infection [Evidence Level A]. If used, indwelling catheters should be assessed daily and removed as soon as possible [Evidence Level A]. Excellent pericare and infection prevention strategies should be implemented to minimize risk of infections [Evidence Level B]. *Refer to Section 4.6(iii) for additional information.*

ii. All stroke patients should be screened for urinary incontinence and retention (with or without overflow), fecal incontinence, and constipation [Evidence Level C].

iii. The use of a portable ultrasound machine is recommended as the preferred noninvasive painless method for assessing post-void residual [Evidence Level C].

iv. Stroke patients with urinary incontinence should be assessed by trained personnel using a structured functional assessment to determine cause and develop an individualized management plan [Evidence Level B].

v. A bladder-training program should be implemented in patients who are incontinent of urine [Evidence Level C], including timed and prompted toileting on a consistent schedule [Evidence Level B].

vi. Appropriate intermittent catheterization schedules should be established based on amount of post-void residual [Evidence Level B].

vii. A bowel management program should be implemented for stroke patients with persistent constipation or bowel incontinence [Evidence Level A].

9.8 Oral Care (no changes for 2018)

i. Upon or soon after admission, all stroke patients should have an oral/dental assessment, including screening for signs of dental disease, level of oral care, and appliances [Evidence Level C].

ii. For patients wearing a full or partial denture it should be determined if they have the neuromotor skills to safely wear and use the appliance(s) [Evidence Level C].

iii. An appropriate oral care protocol should be used for every patient with stroke, including those who use dentures [Evidence Level C]. The oral care protocol should be consistent with the Canadian Dental Association recommendations [Evidence Level B], and should address areas such as frequency of oral care (ideally after meals and before bedtime); types of oral care products (toothpaste, floss, and mouthwash); and management for patients with dysphagia.

iv. If concerns with implementing an oral care protocol are identified, consider consulting a dentist, occupational therapist, speech-language pathologist, and/or a dental hygienist [Evidence Level C].

v. If concerns are identified with oral health and/or appliances, patients should be referred to a dentist for consultation and management as soon as possible [Evidence Level C].

Rationale

Acute stroke is responsible for prolonged lengths of stay compared to other causes of hospitalization in

Canada, and the burden on inpatient resources increases further when complications arise. Acute stroke patients are at risk for complications during the early phase of recovery. The priorities for inpatient care are management of stroke sequelae to optimize recovery, prevention of post-stroke complications that may interfere with the recovery process, and prevention of stroke recurrence. There is weaker to moderate evidence for many of the interventions to accomplish these goals; however, that does not minimize their importance or their contribution to patient outcomes, including length of stay, and complications.

System Implications

1. Standardized evidence-based protocols instituted for optimal inpatient care of all acute stroke patients, regardless of where they are treated in the health care facility (stroke unit or other ward), and across the regional stroke system of care.
2. Ongoing professional development and educational opportunities for all health care professionals who care for acute stroke patients.
3. Referral systems to ensure rapid access to specialty care such as dentistry and hematology.

Performance Measures

1. Percentage of patients admitted to hospital with a diagnosis of acute stroke who experience one or more complications during hospitalization (deep venous thrombosis, pulmonary embolus, secondary cerebral hemorrhage, gastrointestinal bleeding, pressure ulcers, urinary tract infection, pneumonia, seizures [or convulsions]) during inpatient stay.
2. Median length of stay during acute phase of care for all stroke patients admitted to hospital (core). (Stratify by stroke type).
3. Percentage of patients who experienced prolonged length of stay beyond expected length of stay as a result of experiencing one or more complications.
4. Median length of stay during acute phase of care for all stroke patients admitted to hospital that experience one or more complications during hospitalization (core). (Stratify by stroke type and complication type).

Measurement Notes

a. *Refer to the Quality of Stroke Care in Canada Key Quality Indicators and Case Definitions 2018 document for more detailed information.www.strokebestpractices.ca/*
b. Risk adjustment to account for other comorbidities, age, and gender.
c. Length of stay analysis should be stratified by presence or absence of in-hospital complications to look for the impact of a complication on length of stay.
d. Patient and family experience surveys should be in place to monitor care quality during inpatient stroke admissions.

Implementation Resources and Knowledge Transfer Tools

Health Care Provider Information

- Canadian Stroke Best Practices Implementation guide
- Canadian Stroke Best Practice Recommendations Acute Stroke Management Module: Table 2A: Recurrent Stroke Risk Levels and Initial Management
- Canadian Stroke Best Practice Recommendations Acute Stroke Management Module: Table 2B: Recommended Laboratory Investigations for Patients with Acute Stroke or Transient Ischemic Attack

- Canadian Stroke Best Practice Recommendations Acute Stroke Management Module: Appendix Three Screening and Assessment Tools for Acute Stroke Severity
- HSF Stroke Assessment Pocket Cards: http://www.strokebestpractices.ca/wp-content/uploads/2017/07/002-17_CSBP_StrokeAssessPocketGuide_7.5x4.25_EN_v6_LR.pdf
- RNAO Guidelines for Oral Health: http://rnao.ca/bpg/guidelines/oral-health-nursing-assessment-and-intervention
- RNAO Continence Care resources: http://rnao.ca/bpg/guidelines/resources/continence-care-education-selflearning-package
- RNAO Guidelines for Falls Prevention in the Older Adult: http://rnao.ca/bpg/guidelines/prevention-falls-and-fall-injuries
- Canadian Continence algorithms: http://www.canadiancontinence.ca/EN/urinary-incontinence-charts.php
- Canadian Cardiovascular Society Atrial Fibrillation Guidelines 2016: http://www.onlinecjc.ca/article/S0828-282X(16)30829-7/fulltext
- American College of Chest Physicians (ACCP) Guidelines for Diagnosis & Management of DVT / PE, 9th Ed.: http://www.chestnet.org/Guidelines-and-Resources/CHEST-Guideline-Topic-Areas/Pulmonary-Vascular
- Canadian Association of Radiologists 2012 guidelines: https://car.ca/patient-care/practice-guidelines/

Patient Information

- "Your Stroke Journey": http://www.strokebestpractices.ca/wp-content/uploads/2015/03/YOURSTROKEJOURNEY.FINAL_.ENGLISH..pdf
- Canadian Continence Foundation patient resources: http://www.canadiancontinence.ca/EN/health-care-professionals.php
- Heart and Stroke Foundation website, Living with Physical Changes:

  http://www.heartandstroke.ca/stroke/recovery-and-support/physical-changes

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

Summary of the Evidence 2018

Medical complications are relatively common following stroke and are associated with increased lengths of stay and higher cost. Appropriate investigations and management strategies should be implemented for all hospitalized patients to avoid complications, prevent stroke recurrence and improve the odds of a good recovery. Estimates of the percentage of patients who experience at least one medical complication during hospitalization vary widely from 25% (Ingeman et al. 2011) to 85% (Langhorne et al. 2000). Some of the most commonly-cited complications include urinary tract infections, fever, pneumonia, and deep vein thrombosis (Otite et al. 2017, Indredavik et al. 2008, Roth et al. 2001).

Cardiovascular Investigations

Detecting atrial fibrillation (AF) after a stroke or TIA is important since it is a major risk factor for subsequent stroke and, once identified, can be effectively treated. However, AF is under-diagnosed because it is frequently paroxysmal and asymptomatic. Additionally, although many abnormalities can be detected within the first few days of monitoring, prolonged screening may be required to detect others. Flint et al. (2012) followed 239 patients with cryptogenic ischemic stroke who underwent outpatient cardiac monitoring using an electrocardiographic loop recorder for 30 days. Paroxysmal atrial fibrillation (PAF) was detected in 26 patients (11.0%; 95% CI: 7.6% to 15.7%) who were previously

undiagnosed. While PAF was detected most often (45%) in patients within the first 10 days, 31% were detected from day 11 to 20 and 24%, from day 21 to 30. Suissa et al. (2012) included 946 patients with acute ischemic stroke who were previously undiagnosed with AF. Patients were admitted to an intensive stroke unit care that included continuous cardiac monitoring or to a conventional stroke unit care where patients received a baseline ECG, 24-hour Holter monitor and additional ECGs when necessary. Significantly more cases of AF were detected in patients in the continuous cardiac monitoring group (14.9% vs. 2.3%, adj OR=5.29; 95% CI 2.43 to 11.55). The odds of detection were highest within the first 24 hours of monitoring (OR=9.82; 95% CI 3.01 to 32.07). A prospective cohort study that compared the effectiveness of serial ECGs and Holter monitoring for the identification of AF in patients post stroke found that both methods were equally effective in identifying cases that were not present on a baseline assessment (Douen et al. 2008). Together, serial ECG's and Holter monitoring identified 18 new cases of AF after baseline ECG assessment in the 144 patients included in the study. The majority (83%) of these cases were identified within 72 hours. A recent systematic review (Kishore et al. 2014) includes the results from 32 studies (5,038 patients) of patients with acute ischemic stroke or TIA who had undergone invasive or non-invasive cardiac monitoring for a minimum of 12 hours following event. The different types of cardiac monitoring evaluated included inpatient cardiac monitoring, 24, 48 & 72hr and 7-day Holter, external loop recorder, invasive cardiac monitoring and mobile cardiac outpatient telemonitoring. The overall detection rate of AF was 11.5% (95% CI 8.9%-14.3%) and was higher in selected (pre-screened or cryptogenic) patients (13.4%, 95% CI 9.0%-18.4%) compared with unselected patients (6.2%, 95% CI 4.4%-8.3%). The detection rate of AF in cryptogenic stroke was 15.9% (95% CI 10.9%-21.6%).

The use of transesophageal echocardiography (TEE) has been shown to be more sensitive compared with transthoracic echocardiography (TTE) for detecting cardiac abnormalities following ischemic stroke or TIA, although it is costlier and less acceptable to patients. Common TEE findings following stroke have included atheromatosis, patent foramen ovale, atrial septal aneurysm, (Marino et al. 2016, Katsanos et al. 2015). Marino et al. (2016) reported that 42.6% of 263 patients admitted following an acute ischemic stroke had a TEE finding which could explain the etiology of stroke/TIA. De Bruijn et al. (2006) included 231 patients with recent stroke (all types) or TIA whose stroke etiology remained in questions following initial ECG, ultrasound assessments and blood tests. All patients had a TEE followed by a TTE and the identification of major and minor cardiac sources of embolism were compared between the two diagnostic tools. A potential cardiac source of embolism was detected in 55% of the patients. Significantly more abnormalities were identified using TEE. A cardiac source was detected in 39% of patients where TEE was positive and the TTE, negative. A major cardiac risk factor was detected based on TEE in 16% of patients. The detection of possible cardiac sources of embolism was statistically significantly greater using TEE compared to TTE in both patients aged ≤45 years and >45 years.

Venous Thromboembolism Prophylaxis

The use of low molecular weight heparins (LMWH) has been shown to be more effective for the prevention of venous thromboembolism compared with unfractionated heparin (UFH) and is associated with a lower risk of serious bleeding events. A Cochrane review (Sandercock et al. 2008) included the results from 9 RCTs (n= 3,137) of patients with acute ischemic stroke who were randomized within 14 days of stroke onset to receive LMWHs or heparinoids, or UFH for an average of 10 to 12 days. The odds of DVT occurrence during treatment period were lower in the LMWH/heparinoid group (OR=0.55, 95% CI 0.44 -0.70, p<0.0001). There was no difference between groups in mortality during the treatment period or follow-up, nor in the odds of any ICH/hemorrhagic transformation during treatment (OR= 0.75, 95% CI 0.46- 1.23, p=0.25); however, there was an increased risk of major extracranial hemorrhage associated with the UHF group (OR= 3.79, 95% CI 1.30-11.06, p=0.015). The authors cautioned that the event rates for serious events (pulmonary embolus, death and serious bleeding) were too low to provide reliable estimates of the risk and benefits.

In the PREVAIL trial (Sherman et al. 2007), 1,762 patients who had experienced an ischemic stroke within the previous 48 hours and who were immobile with NIHSS (leg) motor scores of ≥2, were randomized to receive 40 mg enoxaparin subcutaneously once daily or 5000U UFH twice daily with

UFH, for 10 days. The risk of all DVT at 14 days was 43% lower among patients receiving enoxaparin (10% vs. 18%, RR= 0.57, 95% CI 0.44 to 0.76, p<0.0001). The incidences of all proximal and distal DVT at 14 days were lower among patients receiving enoxaparin (5% vs. 10%, RR= 0.47, 95% CI 0.31 to 0.72, p=0.0003 and 7% vs. 13%, RR= 0.52, 95% CI 0.37 to 0.74, p=0.0002, respectively). There were no differences between groups in the incidence of symptomatic DVT or PE at 14 days (DVT: <1% vs. 1%, RR=0.29, 95% CI 0.06-1.38, p=0.096; PE: <1% vs. 1%, RR= 0.29, 95% CI 0.02-1.39, p=0.059). The protective effects were maintained at day 30, 60 and 90, following treatment. There were no significant differences between groups in any of the bleeding outcomes: total bleeding events, symptomatic ICH, major extracranial hemorrhage, all-cause mortality at days 14 or 90. In subgroup analysis treatment was effective regardless of time to initiation of prophylaxis, diabetes, obesity, previous stroke, stroke severity (NIHSS score ≥14 vs. < 14), gender or age. Using data from the PREVAIL trial, Pineo et al. (2011) conducted an economic analysis associated with enoxaparin or UFH use in a hypothetical cohort of 10,000 acutely ill medical inpatients. Although the drug cost was higher ($260 vs. $59), enoxaparin was associated with an overall average net savings of $1096 per patient. The cost savings was highest for patients with more severe strokes (NIHSS score≥14). The increased cost of enoxaparin was off-set by the avoidance of additional medical costs associated with reduced event rates of DVT and PE.

Anticoagulants and antithrombotics should be avoided in the early period following intracerebral hemorrhage to reduce the risk of worsening the initial hematoma. Evidence related to the benefit of venous thromboembolism prophylaxis is not as strong for this subgroup of patients. Orken et al. (2009) randomized 75 patients with primary ICH to LMWH (Enoxaparin 40mg/d) or long compression stockings (CS) after the first 48 hours of symptom onset. Hematoma volumes were calculated on the initial and follow-up CTs with the ABC/2 method. There was no evidence of hematoma enlargement at 72 hours, 7 or 21 days in either group. In addition, no other systemic bleeding complications were observed in the LMWH group. Four asymptomatic DVTs were detected (3 in LMWH and 1 in CS group). Investigators calculated the rate of asymptomatic DVT and PE in ICH patients, at 4% and 2.5% in the LMWH group. Tetri et al. (2008) reviewed the charts of 407 patients admitted for ICH patients, of whom 232 had received anticoagulant therapy for DVT prophylaxis using enoxaparin. Three-month mortality was similar between groups-19% in the treated group compared to 21% in the group who did not receive prophylaxis. Hematoma enlargements occurred in 9% and 7% of the treated and untreated patients, whereas symptomatic venous thromboembolic complications were observed in 3% and 2% of patients, respectively.

The use of external compression stockings/devices have been investigated in a series of three large, related RCTs, the Clots in Legs Or sTockings after Stroke (CLOTS) trials. In CLOTS 1 (Dennis et al. 2009), 2,518 patients, admitted to hospital within 1 week of acute ischemic stroke or ICH and who were immobile were randomized to either routine care plus thigh-length graded compression stockings (GCS) or to routine care plus avoidance of GCS. Patients wore the garments day and night until they became mobile, were discharged, or there were concerns with skin breakdown. At 30 days there was no significant difference between groups in the incidence of proximal DVT (GCS 10.0% vs. avoid GCS 10.5%). GCS use was associated with a non-significant absolute reduction in risk of 0.5% (95% CI -1.9% to 2.9%). The incidence of any DVT or PE was non-significantly lower in the GCS group (17.0% vs. 18.4%, OR=0.91, 95% CI 0.74-1.11), but the frequency of skin ulcers or breakdown were significant higher in the GCS group (5.1% vs. 1.3%, OR=4.18, 95% CI 2.40-7.27). The inclusion criteria for the CLOTS 2 trial (The CLOTS Trials Collaboration 2010) were similar to those of CLOTS 1. In this trial, 3,114 patients were randomized to wear thigh-length stockings or below-knee stockings while they were in the hospital, in addition to routine care, which could have included early mobilization, hydration, and/or the use of anticoagulants/antiplatelets. At 30 days, there was a significant reduction in the incidence of proximal DVT associated with thigh-length GCS (6.3% vs. 8.8%, adj OR=0.69, 95% CI 0.53-0.91, p=0.008). The incidence of asymptomatic DVT were also lower in the thigh length GCS group (3.2% vs. 4.8%, adj OR=0.64, 95% CI 0.44-0.93, p=0.02). The use of thigh-length GCS was associated with an increased risk of skin breakdown (9.0% vs. 6.9%, OR=1.33, 95% CI 1.031.73, p=0.03). Finally, in CLOTS 3 (Dennis et al. 2013) 2,876 patients were randomized to wear thigh length intermittent pneumatic compression (IPC) device or to no IPC at all times except for washing and therapy, for a minimum of 30 days. The mean duration of IPC use was 12.5 days and 100% adherence to treatment

was achieved in only 31% in the IPC group. The incidence of proximal DVT within 30 days was significantly lower for patients in the IPC group (8.5% vs. 12.1%, OR=0.65, 95% CI 0.51-0.84, p=0.001, ARR=3.6%, 95% CI 1.4%-5.8%). There were no significant differences between groups for the outcomes of: death at 30 days (10.8% vs. 13.1%, p=0.057), symptomatic proximal DVT (2.7% vs. 3.4%, p=0.269), or PE (2.0% vs. 2.4%, p=0.453). The incidence of any DVT (symptomatic, asymptomatic, proximal or calf) was significantly lower for IPC group (16.2% vs. 21.1%, OR=0.72, 95% CI 0.60-0.87, p=0.001). Skin breakdown was more common in IPC group (3.1% vs. 1.4%, OR=2.23, 95% CI 1.31-3.81, p=0.002). At 6 months, the incidence of any DVT remained significantly lower in the IPC group (16.7% vs. 21.7%, OR=0.72, 95% CI 0.60-0.87, p=0.001). The incidence of any DVT, death or PE also remained significantly lower for IPC group (36.6% vs. 43.5%, OR=0.74, 95% CI 0.63-0.86, p<0.0001).

Temperature Management

Elevated body temperature in the early post-stroke period has been associated with worse clinical outcomes. A meta-analysis conducted by Prasad & Krishnan (2010), including the results from six studies demonstrated that fever within the first 24 hours of ischemic stroke onset was associated with twice the risk of short-term mortality (OR= 2.20, 95% CI 1.59–3.03). Fever may result from a secondary infection, such as pneumonia, or may have occurred as a cause of stroke (e.g. infective endocarditis). While interventions to reduce temperature may improve the viability of brain tissue and/or prevent other medical complications post stroke, efforts to reduce fever, through a wide range of modalities, including pharmacological agents, (paracetamol) and physical interventions (cooling blankets and helmets and endovascular treatments) have not been convincingly shown to be effective in reducing/avoiding poorer outcomes.

Frank et al. (2013) conducted a retrospective study of 6,015 ischemic stroke patients who were registered in Virtual International Stroke Trials Archive (VISTA). Patients who received paracetamol for the management of pain (n=1626) or fever (n=809) were compared to those who had not received the medication. In patients treated with paracetamol for fever or pain, there was no difference in the distribution of mRS scores at 90 days, the primary outcome, compared with patients who did not receive treatment, while the odds of pneumonia were significantly reduced (OR=0.73, 95% CI 0.56-0.94, p=0.017). However, among patients without pain or fever who were treated with paracetamol as a prophylactic measure, the odds of poor outcome were increased (mortality at 90 days: OR=1.59, 95% CI 1.13-2.23, p=0.008, mRS score 0-2: OR=0.55, 95% CI 0.41-0.74, p<0.001 and recurrent stroke within 7 days: OR=3.57, 95% CI 1.37-9.32, p=0.009). The largest trial examining the use of pharmacological agents for the reduction of fever was Paracetamol (Acetaminophen) In Stroke (PAIS) trial (den Hertog et al. 2009). In this trial, 1,400 patients were randomized to receive 1 gram paracetamol, 6x daily for 3 days or placebo within 12 hours of symptom onset. While treatment with paracetamol did significantly lower body temperature by a mean of 0.26 °C, it was not associated with improvement beyond expectation (adjusted OR=1.20, 95% CI 0.96-1.50), the increased odds of a favourable outcome, or significant increases in QoL. Treatment with paracetamol was associated with a decrease in 14-day mortality (OR=0.60, 95% CI 0.36-0.90), but there was no difference at 3 months (OR=0.90, 95% CI 0.68-1.18). The PAIS 2 trial (De Ridder et al. 2017) was terminated after enrolling 26 of 1,500 planned patients. In this trial, high-dose (2 grams) or placebo was given for 3 days to patients with a temperature of ≥ 36.5o C. There was no significant difference between groups in the shift in mRS scores at 90 days associated with paracetamol (common adj OR=1.15, 95% CI 0.74-1.79). In a Cochrane review (den Hertog et al. 2009) included the results from 8 RCTs, 5 of which examined pharmacological agents (paracetamol, n=3, metamizole n=1, ibuprofen placebo n=1) versus placebo. Pharmacological treatment significantly reduced temperature at 24 hours following treatment (MD= -0.21, 95% CI -0.28, -0.15, p<0.0001), but was not associated with a reduction in the odds of death or dependency at 1-3 months (OR= 0.92, 95% CI 0.59- 1.42, p=0.69).

In terms of physical methods to reduce fever, the feasibility of endovascular and surface cooling strategies was examined in the COOLAID trial (Oversen et al. 2013). In this trial, 31 patients admitted to an ICU in two hospitals with acute ischemic stroke were randomized to receive therapeutic hypothermia (TH) using endovascular or surface methods, or standard supportive care (n=14). Patients in the TH group had body temperature lowered to 33 degrees C and were maintained for 24 hours, while patients

in the standard care group received acetaminophen if body temp exceeded 37.5 degrees C. There were significantly more episodes of bradycardia associated with the TH group, and a non-significant increase in the incidence of pneumonia (6 vs. 1, p=0.09), although there were no significant differences between groups in other cardiac adverse events or pulmonary adverse events, or death. The authors concluded that the treatment was feasible, but associated with serious complications, particularly in anesthetized patients receiving endovascular cooling. A Health Technology Assessment (Harris et al. 2012) examined the use of any form of non-invasive head cooling following TBI, and cardiac arrest. The most effective techniques for which there were adequate data (nasal coolant and liquid cooling helmets) indicated that intracranial temperature could be reduced by 1 °C in 1 hour.

Mobilization

Early mobilization post stroke is intended to reduce the risk of medical complications including deep vein thrombosis, pressure sores, painful shoulders, and respiratory infections. The potential benefits of early mobilization have been examined in several RCTs, with ambiguous results. One of the sources of variability among studies examining the issue, which may account for conflicting results, is differences in treatment contrasts. Early mobilization was defined as early as 12 hours following stroke to as long as 52 hours, while patients in the delayed group were mobilized from time periods ranging from 48 hours to 7 days. Small sample sizes (i.e. under- powered samples sizes) may also have contributed to null findings. In the Akerhus Early Mobilization in Stroke Study (AKEMIS) 65 patients were randomized to a very early mobilization (VEM) group or to a control group following ischemic or hemorrhagic stroke. Patients in both groups received standard stroke unit care. Patients in the VEM group were mobilized as soon as possible (within 24 hours post stroke), while patients in the control group were mobilized between 24 and 48 hours. The median time to first mobilization from stroke onset was significantly shorter for patients in the VEM group (13.1 vs. 33.3 hrs, p<0.001); however, there were no significant differences between groups on any of the outcomes of interest, including poor outcome at 3 months (mRS score of 3-6), death or dependency, dependency, or number of complications at 3 months. Diserens et al. (2011) randomized 50 patients with ischemic stroke to either an “early mobilization” group who were mobilized out of bed after 52 hour or to a “delayed mobilization” group where patients were mobilized after 7 days. While there were significantly fewer severe complications among patients in the early mobilization group (8% vs. 47%, p < 0.006), there were no significant differences between groups in the numbers of minor complications, neurological deficits, or blood flow modifications.

Several publications are associated with the A Very Early Rehabilitation Trial for Stroke (AVERT) trial. The safety and feasibility of an early mobilization intervention was established by Bernhardt et al. (2008) in Phase I. 71 patients were randomized to receive either very early and frequent mobilization (upright, out of bed, activity – 2x/day, for 6 days a week until discharge beginning within 24 hours of stroke), or usual multi-disciplinary stroke team care. There was a non-significant increase in the number of patient deaths in the early mobilization vs. delayed mobilization group at 3 months (21% vs. 9%, absolute risk difference = 12.0%, 95% CI, 4.3% to 28.2%, p=0.20). After adjusting for age, baseline NIHSS score and premorbid mRS score, the odds of experiencing a good outcome were significantly higher at 12 months for the VEM group (OR= 8.15, 95% CI 1.61-41.2, p<0.01), although not at 3 or 6 months. In AVERT II, examining medical complications associated with very early mobilization (VEM), Sorbello et al. (2009) reported there were no differences in the total number of complications between groups. Severe complications or stroke-related complications occurred in 91 patients in the control group compared with 87 in the VEM group. Cumming et al. (2011) reported that patients in the VEM group returned to walking significantly sooner than patients in the standard care group (median of 3.5 vs. 7.0 days, p=0.032). While there were no differences between groups in proportions of patients who were independent in ADL, or who experienced a good outcome at either 3 or 12 months, VEM group assignment was a significant, independent predictor of independence in ADL at 3 months and of good outcome at both 3 and 12 months. Pooling the results from both the AVERT and VERITAS trials, which used similar protocols for early mobilization, Craig et al. (2010) reported that, compared with patients receiving standard care, patients in the VEM group were more likely to be independent in activities of daily living at

3 months (OR= 4.41, 95% CI 1.36-14.32), and were less likely to experience immobility related complications (OR= 0.20, 95%CI 0.10-0.70). The most recent replication of AVERT examined the effectiveness of a protocol of more intensive, early out-of-bed activity. Bernhardt et al. (2015) randomized 2,104 adults (1:1) to receive early mobilization, a task-specific intervention focused on sitting, standing, and walking activity, initiated within 24 hours of stroke onset, or to usual care for 14 days (or until hospital discharge). The median time to first mobilization was significantly earlier in the early mobilization group (18.5 vs. 22.4 hrs, p<0.0001). Patients in the early mobilization group received significantly more out of bed sessions (median of 6.5 vs. 3, p<0.0001) and received more daily therapy (31 vs. 10 min, p<0.0001). However, significantly fewer patients in the early mobilization group had a favourable outcome, the primary outcome, defined as mRS 0-2, at 3 months (46% vs. 50%; adjusted OR=0.73, 95% CI 0.59-0.90, p=0.004). There were no significant differences between groups for any of the secondary outcomes (shift in distribution of mRS, time to achieve assisted- free walking over 50m, proportion of patients able to walk unassisted at 3 months, death or serious adverse events), nor were any interactions identified based on pre-specified sub groups for the primary outcome (age, stroke type, stroke severity, administration of t-PA, or geographical region of recruitment). Further analysis of AVERT data (Bernhardt et al. 2016), controlling for age and stroke severity, suggested that shorter, more frequent mobilization early after acute stroke was associated with improved odds of favorable outcome at 3 months, while increased amount (minutes per day) of mobilization reduced the odds of a good outcome.

Nutrition and Dysphagia

A standardized program for screening, diagnosis and treatment of dysphagia following acute stroke results has been shown to reduce the incidence of pneumonia and feeding tube dependency. Bedside screening may include components related to a patient's level of consciousness, an evaluation of the patient's oral motor function and oral sensation, as well as the presence of a cough. It may also include trials of fluid. Coughing during and up to one minute following test completion and/or "wet" or hoarse voice are suggestive of an abnormal swallow. Silent aspiration may occur in patients who do not cough or complain of any problems with swallowing or have no wet-sounding voice, highlighting the importance of dysphagia screen for all patients acutely following stroke.

Hinchey et al. (2005) evaluated adherence to screening for dysphagia and associated pneumonia among individuals with ischemic stroke in the United States and reported that pneumonia occurred less frequently among those who had received a dysphagia screen (2.4% vs. 5.4%). Similar results were found in a study by Lakshminarayan et al. (2010) in which unscreened patients were found to have a greater risk of developing pneumonia than patients who had passed a screen for dysphagia (OR=2.2; 95% CI 1.7-2.7). In contrast to these two studies suggesting that screening is associated with a lower incidence of pneumonia, Masrur et al. (2013) reviewed the records of 314,007 patients with ischemic stroke admitted to hospitals participating in the Get-with-the-Guideline Registry. The outcomes of patients who had received a standardized swallowing screen including bedside or instrumental methods, were compared with those of patients who had not been screened. 68.9% patients were screened for dysphagia, while 31.1% were not. Of the 5.7% of patients who developed post-stroke pneumonia within 48 hours of admission, patients who were screened for dysphagia were more likely to develop pneumonia compared with those who did not develop pneumonia (7.5% vs. 68.5%, p<0.001). This finding suggests that patients who were perceived to be at high risk of dysphagia/aspiration may have been screened preferentially compared with patients perceived to be at low risk. To wit, Joundi et al. (2017) reported that patients with mild strokes were less likely to be screened compared with those with moderate strokes (adj OR=0.51, 95% CI 0.41-0.64) using data from 6,677 patients included in the Canadian Stroke Registry.

Middleton et al. (2011), in a multi-centered cluster RCT including 19 large tertiary care facilities with acute stroke units, randomized 4,198 patients to receive care at institutions that had adopted nursing protocols to identify and manage 3 complications- hyperglycemia, fever and swallowing dysfunction or to a control facility. The dysphagia component included education and training in the use of the ASSIST screening tool. While the intervention was associated with a decreased frequency of death or dependency at 90 days (42% vs. 58%, p=0.002) and swallowing screening was performed more

frequently in the intervention group (46% vs. 7%, p<0.0001), there was no difference between groups in the incidence of pneumonia (2% vs. 3%, p=0.82). Using UK registry data, Bray et al (2017) reported a higher risk of stroke-associated pneumonia (SAP) with increasing times to dysphagia screening and assessment. The overall incidence of SAP was 8.7% (13.8% for patients not screened, 8.0% for patients who were screened and 14.7% for patients who received a comprehensive assessment). Independent predictors of receiving a dysphagia screen have been reported to include older age, admission to specialized units, the presence of weakness, increased stroke severity, speech difficulties and treatment with thrombolysis (Joundi et al. 2017, Mansur et al. 2013).

The effectiveness of a variety of treatments for dysphagia management was recently the subject of a Cochrane review (Geeganage et al. 2012). The results from 33 RCTs examining acupuncture, behavioral interventions, drug therapy, neuromuscular electrical stimulation, pharyngeal electrical stimulation, physical stimulation, (thermal, tactile) transcranial direct current stimulation and transcranial magnetic stimulation, were included. Pooling of results was not possible for many of the outcomes due to small numbers of studies available evaluating similar interventions/outcomes. Death or dependency at end of trial was the primary outcome, although only two RCTs were included in the pooled result. The results were not significant (OR=1.05, 95% CI 0.63 to 1.75, p=0.86). Acupuncture and behavioural modifications were associated with reduction in the presence of dysphagia at the end of treatment. No significant treatment effect was associated with subgroup analysis by therapy type (behavioral interventions, drug therapy, and electrical stimulation) for the outcome of chest infections.

Dietary modifications, including altered textured solids and fluids and the use of restorative swallowing therapy, and compensatory techniques, are the most commonly used treatments for the management of dysphagia in patients who are still safe to continue oral intake. Unfortunately, there is little evidence direct evidence of their benefit. Carnaby et al. (2006) randomized 306 patients with dysphagia admitted to hospital within 7 days of acute stroke, to receive usual care, standard low-intensity intervention (composed of environmental modifications, safe swallowing advice and appropriate dietary modifications), or standard high-intensity intervention and dietary prescription (daily direct swallowing exercises, dietary modification), for up to one month. When the results from the high-intensity and low-intensity groups were combined and compared with the usual care group, patients in the active therapy group regained functional swallow sooner and had a lower risk of chest infections at 6 months.

Oral supplementation can be used for patients who are not able to consume sufficient energy and protein to maintain body weight, or for those with premorbid malnutrition. The FOOD trial (Dennis et al. 2005a) aimed to establish whether routine oral nutritional supplementation in patients who could safely swallow and were prescribed a regular hospital diet, was associated with improved outcome after stroke. 4,023 patients were randomized to receive or not receive an oral nutritional supplement (540 Kcals) in addition to a regular hospital diet, provided for the duration of their entire hospital stay. At 6-month follow-up, there were no significant differences between groups on the primary outcome of death or poor outcome (OR=1.03, 95% CI 0.91 to 1.17, p>0.05). The absolute risk of death or poor outcome was 0.7%, 95% CI -2.3 to 3.8. Only 314 (8%) patients were judged to be undernourished at baseline. The anticipated 4% absolute benefit for death or poor outcome from routine oral nutritional supplements was not evident. The FOOD trial results would be compatible with a 1% to 2% absolute benefit or harm from oral supplements. Results from RCTs examining nutrition-related outcomes suggest that oral supplements can increase the amount of energy and protein patients consume, and prevent unintentional weight loss (Gariballa et al. 1998, Ha et al. 2010).

For patients who cannot obtain nutrient and fluid needs orally, enteral nutrition may be required. The decision to use enteral support should be made within the first seven days post stroke. The largest trial that addresses both the issues of timing of initiation of enteral feeding and the choice of feeding tube was the FOOD trial (Dennis et al. 2005b), which included 1,210 patients admitted within 7 days of stroke from 47 hospitals in 11 countries. In one arm of the trial, patients were randomized to receive either a percutaneous endoscopic gastrostomy (PEG) or nasogastric (NG) feeding tube within 3 days of enrolment into the study. PEG feeding was associated with an absolute increase in risk of death of 1.0% (–10.0 to 11.9, p=0.9) and an increased risk of death or poor outcome of 7.8% (0.0 to 15.5, p=0.05) at 6

months. In the second part of the trial patients were randomized to receive feeds as early as possible or to avoid feeding for 7 days. Early tube feeding was associated with non-significant absolute reductions in the risk of death or poor outcome (1.2%, 95% CI -4.2 to 6.6, p=0.7) and death (15.8%, 95% CI -0.8 to 12.5, p=0.09) at 6 months.

Seizure Management

The incidence of post-stroke seizure ranges from 5%-15%, depending on stroke etiology, severity, and location (Gilad, 2012). Hemorrhagic events and cortical lesions are associated with the highest risk of both first and recurrent seizure (Gilad et al. 2013). Evidence examining the effectiveness of pharmacological treatment for post- stroke seizures is limited. A recent Cochrane review (Sykes et al. 2014) sought studies including patients of any age recovering from ischemic stroke or ICH, suffering from any seizure type that evaluated antiepileptic drugs compared with a placebo or no drug for the primary and secondary prevention of post stroke seizures. Only a single trial (Gilad et al. 2011) was found. In this trial, 84 patients with spontaneous non-traumatic and non-aneurysmatic ICH were randomized to receive 800 mg/day valproic acid or placebo daily for one month, for primary seizure prophylaxis. At 1 year, there were 15 cases of new seizure. There were no differences in early (within 14 days of randomization) or late (>14 days) seizure between treatment groups (1 vs. 4, p=0.8 and 6 vs. 4, p=0.5, respectively). Van Tuijl et al. (2011) planned to recruit 200 patients with lobar ICH or ischemic stroke, with a cortical syndrome and mRS≥3 or NIHSS ≥6. Patients were to be randomized to receive either 1500 mg of levetiracetam daily or placebo, within 2 to 7 days following acute stroke for primary seizure prevention. Treatment was scheduled to continue for 12 weeks. The trial was stopped prematurely due to a failure to recruit sufficient numbers of patients. At the point the trial was stopped, only 16 patients had been recruited over a period of 16 months.

The use of antiepileptic medications for the secondary prevention of seizures has also been examined, although placebo-controlled trials are absent. Gilad et al (2007) randomized 64 elderly patients admitted to a neurological department after stroke who had experienced a first seizure to receive either lamotrigine (100 mg BID) or carbamazepine (300 mg BID). The number of patients who were seizure free at 12 months was non-significantly higher in the lamotrigine group (23 vs. 14, p=0.06). The total number of adverse events was significantly higher in the carbamazepine group (12 vs. 2, p=0.05), as was the number of withdrawals for adverse events (10 vs. 1, p=0.02).

Continence

To avoid the onset of urinary tract infections (UTIs), the use of indwelling catheters is largely discouraged in clinical settings and is typically limited to patients with incontinence that cannot be managed any other way. If used, the catheter should be changed or removed as soon as possible. Ersoz et al. (2007) reported that among 110 patients consecutively admitted for rehabilitation following stroke, 30 developed a symptomatic UTI during hospitalization. UTIs occurred more frequently in patients with indwelling catheters, compared with patients who could void spontaneously (7/14 vs. 23/96, p=0.041) and in patients with residual urine volumes of >50 mL (41.2% vs. 19.5%, p=0.039). Several infection prevention strategies that have been identified to prevent or delay the onset of catheter-associated UTIs include inserting the catheter using aseptic technique, correctly positioning the drainage tube and the collection bag, maintaining uncompromising closed drainage, achieving spontaneous voiding, and administering intermittent catheterizations.

The effectiveness of bladder-training programs, which typically include timed/prompted voiding, bathroom training, pelvic floor exercises, and/or drug therapy, has been evaluated in a small number of studies. In one, 42 patients admitted to a single acute stroke unit, were each patient was prescribed an individualized bladder program consisting of bladder scanning, intermittent catheterizations/ post-void residual regimen, non-invasive voiding strategies (e.g. pelvic muscle exercises) and/or drug therapy. The regimen was continued until the post-void urine residual was below 100 ml for three consecutive days (Chan et al. 2007). Eighty-four percent of all patients achieved urinary continence within the first month of stroke. Among this group, all females became continent, while 23% of the male patients did not. In a Cochrane review, Eustice et al. (2000) included the results of 9 RCTs (n= 674), examining the potential benefit of prompted voiding (vs. no prompted voiding) provided for 10 days-13 weeks.

Prompted voiding was associated with a reduction in the number of incontinent episodes in 24 hours (MD= -0.92, 95% CI -1.32 to -0.53, p<0.0001). In another Cochrane review examining a broad range of treatments for urinary incontinence, including behavioral interventions, specialized professional input, complementary medicine, pharmacotherapy and physical therapy, Thomas et al (2008) reported that treatment was associated with a decreased risk of urinary incontinence (RR= 0.44, 95% CI 0.23-0.86, p=0.0017). The mean improvement in FIM bladder score of 35 women with stroke who were admitted to a rehabilitation unit following the implementation of a standardized bladder management program was significantly greater (2.8 vs. 1.6, p=0.01) than those who had been admitted prior to the initiation of the program (Cournan 2012). Thomas et al. (2014) conducted a cluster feasibility trial, *Identifying Continence Options after Stroke (ICONS).* Compared with usual care, the systematic voiding program was not associated with significantly increased odds of being continent at 6 or 12 weeks.

Oral Care

Physical weakness following stroke may prevent patients from independently completing their activities of daily living, including oral care. Poor oral care, combined with potential side effects of medication (e.g., dry mouth, oral ulcers, stomatitis), may contribute to a greater amount of bacteria in the mouth, leading to the development of pneumonia. Patients have also reported lower oral health-related quality of life as a result of poor or inadequate dental care following stroke (Schimmel et al. 2011). Therefore, on admission to hospital, all patients should have an oral/dental assessment to examine mastication, tooth wear, disease and use of appliances, following stroke.

However, few studies have examined interventions to improve oral hygiene in patients following a stroke. Kim et al. (2014) reported that patients admitted to a neurosurgical ICU and randomized to an intervention group that received daily oral hygiene had lower Plaque Index and Gingival Index scores, compared with patients in a control group. Lam et al. (2013) included 102 dentate patients admitted to a rehabilitation unit following ischemic stroke or ICH within the previous 7 days, with a Barthel index score of <70. Patients were randomized to receive oral hygiene instruction (OHI), + chlorhexidine (CHI) mouth rinse, or OHI + CHI + assisted tooth brushing, twice daily for 3 weeks. The mean plaque index and Gingival Bleeding Index scores of patients in the OHI+CHX and OHI+CHX+assisted brushing groups were improved significantly more than patients that only received instruction on oral hygiene. A Cochrane review conducted by Brady et al. (2006) included the results of 3 RCTs (n=470) that included patients receiving some form of assisted oral health care (OHC) within a healthcare facility. Treatments evaluated included oral health care plus timed tooth brushing, health care education and selective decontamination of digestive tract using an antimicrobial gel applied to the mucous membranes of the mouth several times per day. Due to the small number of studies and variability in treatments, pooled analyses were not possible. The use of decontamination gel was associated with a reduction in the incidence of pneumonia: (OR=0.20, CI 95% 0.05 to 0.84, p = 0.03). A single education session was not associated with a reduction in dental plaque tooth coverage, the presence of gingivitis, or denture-induced stomatitis at one or 6 months following training, but was associated with a significant reduction in denture plaque at both assessment points and higher knowledge scores among care providers.

Reference List and Evidence Tables

Evidence Table 2 and References available on website at www.strokebestpractices.ca

Section 10: Advance Care Planning (Sixth Edition, 2018)

10. Advance Care Planning Recommendations

Definition: An advanced care plan is defined as written communication by a competent individual imparting their preferences regarding potential future healthcare decisions. These plans are to be referred to in the event of future incapacity of said individual.

An advance care plan can involve two key factors: "Instructional Directives" and "Proxy Directives". According to the Health Law Institute[1]:

"Instructional directives state what (or how) health care decisions are to be made when you are unable to make these decisions yourself. This type of directive may set out specific instructions or it may set out general principles to be followed for making your health care decisions. Instructional advance directives are also known as 'living wills'. Proxy directives specify who you want to make decisions for you when you are no longer able to make the decisions yourself" (Health Law Institute, 2018). This designation is also known as 'power of attorney' or 'substitute decision maker'.

Health Law Institute, Dalhousie University. *End of Life Law and Policy in Canada: Advance Directives* [Internet]. 2018. Available from: http://eol.law.dal.ca/?page_id=231

10.0 Patients surviving a stroke, as well as their families and informal caregivers, should be approached by the stroke health care team to participate in advance care planning [Evidence Level C].

i. The primary goal of advance care planning conversations is to prepare patients and substitute decision makers for providing consent in future situations (for example, in light of recent significant illness such as stroke) [Evidence Level B].

   a. Advance care planning may include identifying a substitute decision-maker (proxy, agent or Power of Attorney), and discussion of the patient's personal values and wishes which they can apply in future if the need arises to make medical decisions or provide consent on behalf of the patient [Evidence Level B].

   b. Advance care planning discussions should be documented and reassessed regularly with the active care team and substitute decision-maker [Evidence Level C].

ii. The advance care planning conversation should be revisited periodically, such as when there is a change in the patient's health status [Evidence Level B].

iii. The interdisciplinary team should have the appropriate communication skills and knowledge to address the physical, spiritual, cultural, psychological, ethical, and social needs of stroke patients, their families, and informal caregivers [Evidence Level C].

   a. Respectful discussion of patient's values and wishes should be balanced with information regarding medically appropriate treatment related to ongoing stroke management and future medical care [Evidence Level C].

iv. Capacity related provincial legislation should be reviewed and appropriate substitute decision makers should be identified if a survivor is deemed incapable of making specific decisions re: their personal health care and/or discharge related finances [Evidence Level C].

Rationale

Advance care planning is a process through which a patient in consultation with health care providers and family members make decisions regarding their health care, should they become incapable of participating in decision making. Often in patients with stroke, the direction of these decisions is unclear for the family when the patient is unable to participate in decision-making. Advance care planning is an important educational aspect of any patient encounter when a serious or chronic condition is involved, where the risks of a recurrent event are increased, such as with stroke.

System Implications

1. Protocols for advance care planning to elicit patient and family goals for care preferences, and ensure these are documented and communicated to decision makers and health care team members.
2. Information on advance care planning and linkages to local stroke support organizations and their services should be available for staff to share with patients and families.
3. Communication training for physicians, nurses, and allied health professionals that addresses supporting patients and their families through advance care planning.

Performance Measures

1. **Percentage of stroke patients who have been approached to participate in advance care planning and/or who have a documented conversation with a health care provider about resuscitation, hydration, and/or feeding preferences.**
2. Percentage of stroke patients who identify a substitute decision-maker.
3. Percentage of stroke patients who complete a personal or advance care directive documented on their chart.
4. Percentage of patients with advance care plans whose actual care was consistent with the care defined in their advance care plan.

Measurement Notes

a. Documentation for the advance care plan measures may appear in consult notes, nursing notes, or physician notes.

b. A copy of the advance care plan may be included in the patient's chart.

c. Data quality may be an issue with some of these performance measures. Improved documentation should be promoted among health care professionals.

d. Patient and family experience surveys should be in place to monitor care quality with end-of life situations.

Implementation Resources and Knowledge Transfer Tools

Health Care Provider Information

- Advance Care Planning in Canada: http://www.advancecareplanning.ca/
- Patient Rights Booklet: https://elplanning.ca/advance-care-planning-toolkit/
- Patient Rights Booklet: https://d3n8a8pro7vhmx.cloudfront.net/dwdcanada/pages/709/attachments/original/1474555815

/patient-rights-booklet_2016_elpc1.pdf?1474555815

- Canadian Hospice Palliative Care Association Advance Care Planning Resource Commons: http://www.chpca.net/resource-commons/advance-care-planning-resource-commons.aspx
- Canadian Virtual Hospice: http://www.virtualhospice.ca/en_US/Main+Site+Navigation/Home/Topics/Topics/Decisions/Advance+Care+Planning+Across+Canada.aspx

Patient Information

- "Your Stroke Journey": http://www.strokebestpractices.ca/wp-content/uploads/2015/03/YOURSTROKEJOURNEY.FINAL_.ENGLISH..pdf
- Advance Care Planning in Canada: http://www.advancecareplanning.ca/
- Advance Care Planning Kit: https://elplanning.ca/advance-care-planning-toolkit/
- Canadian Hospice Palliative Care Association Advance Care Planning Resource Commons: http://www.chpca.net/resource-commons/advance-care-planning-resource-commons.aspx
- Canadian Virtual Hospice: http://www.virtualhospice.ca/en_US/Main+Site+Navigation/Home/Topics/Topics/Decisions/Advance+Care+Planning+Across+Canada.aspx
- Post-stroke Checklist: http://www.strokebestpractices.ca/wp-content/uploads/2014/06/HSF%20Post%20Stroke%20Checklist_WEB.pdf

Summary of the Evidence 2018

Advance care planning is a process through which a patient in consultation with health care providers and family members make decisions regarding their health care, should they become incapable of participating in decision making. Elements of advance care planning include the patients' prognosis, treatment options, goals of care, and the identification and documentation of end-of-life wishes. Unfortunately, there is some evidence that the adherence with stated and documented end-of-life preferences may be poor. In a prospective study (Heyland et al. 2013) included 278 elderly patients admitted to 12 hospitals, who were at high risk of dying in the next 6 months and their family members (n=225). Patients and family members were interviewed 2-5 days following admissions related to advanced pulmonary, cardiac, or liver disease, and metastatic cancer. When the medical records were reviewed immediately following the interview, among the 199 patients who had expressed end-of-life care preferences and had a documented goals-of-care order, there was crude agreement between the documented preferences and the patient's stated preferences in only 30.2% of cases. Of the 276 patients who had expressed a preference for care, 77 (27.9%) did not have a written order in the record stating the goal of care. Of these, only 12 (15.6%) preferred aggressive medical management, including resuscitation. The area of poorest agreement was between the stated (28.1%) and documented (4.5%) preference for comfort measures.

Green et al. (2014) used participant observation and semi-structured interviews to gather information from 14 patients, recruited from an acute stroke unit and 2 rehabilitation units and 4 healthcare professionals (HCP), that was related to the communication processes regrading advance care planning (ACP). Four key themes emerged related to why/why not participants engaged in the ACP process: i) lack of perceived urgency by participants, many of whom felt the physician and/or family members would make decisions in accordance with their wishes; ii) a lack of initiation by HCPs to discuss issues around ACP; ii) HCPs expressed hesitation about initiating discussions related to ACP, and uncertainty as the best timing for such discussions. There was also a lack of awareness as to what ACP is, and thought it

was outside their scope of practice and iv) confusing ACP with advance directives, designation of care and living wills.

Although no stroke-specific studies have been published that examine the effectiveness of advance care planning, several exists that include patients with mixed diagnoses. Results from a small number of studies suggest that interventions aimed at increasing advance care planning have been successful in significantly increasing the likelihood that end-of-life wishes are known and respected. In a study of 309 patients admitted to internal medicine, cardiology, or respiratory medicine, Detering et al. (2010) randomized patients to receive formal advance care planning from a trained facilitator or usual care. The intervention was based on the Respecting Patient Choices model, which involves reflection on goals, values, and beliefs, documentation of future health care wishes, and appointment of a surrogate decision maker. Of those who died, end-of life wishes were significantly more likely to be known and respected for participants in the intervention group compared with those in the control group (86% vs. 30%, $p<0.01$). Following the death of a loved one, family members of those in the intervention group reported significantly less anxiety and depression and more satisfaction with the quality of their relative's death, compared to control group family members. Kirchhoff et al. (2012) randomized 313 patients (and their surrogate decision makers) with congestive heart failure or end-stage renal disease who were expected to experience serious complication or death within 2 years, to receive a patient-centered advance care planning intervention or usual care. The intervention was composed of a 60 to 90-minute interview with a trained facilitator to discuss disease-specific end-of-life care issues and options and documentation of treatment preferences. 110 patients died within the study period, of which 26% required a surrogate decision maker at the end-of-life. Only a single patient in the intervention group and 3 in the control group received end-of-life care that was contrary to their wishes for reasons other than medical futility. With respect to resuscitation preferences, non-significantly fewer patients in the intervention group received care that was contrary to their wishes (1/62 vs. 6/48).

Reference List and Evidence Tables

Evidence Table 3 and References available on website at www.strokebestpractices.ca

Section 11: Palliative and End-of-Life Care (Sixth Edition, 2018)

11. Palliative and End-of-Life Care

Definitions:

Palliative care *is an approach that focuses on comfort and quality of life for those affected by life-limiting illness, such as large hemispheric strokes, and severe hemorrhagic stroke. It aims to prevent and relieve physical, social, psychological, or spiritual suffering of stroke patients, their families and informal caregivers. Palliative care can complement life-prolonging or disease-modifying therapies post-stroke and need not be reserved for those whose death is imminent.*

A palliative approach to care *refers to palliative care that is provided by non-palliative care specialists i.e. the basic symptom management and basic psychosocial care that all clinicians provide to patients and their families.*

End-of-life care *is part of the palliative approach and is the management and treatment of dying patients, as well as their families and informal caregivers. The end-of-life period often involves a period of change (e.g. worsening functional status) rather than an acute event.*

Goals of Care for Palliative Care: *In the event of a potentially poor prognosis, the medical team may initiate a 'goals of care' discussion with the individual and/or their substitute decision maker. This conversation would have the objective of establishing consensus on a direction of care and would incorporate the individual's previous wishes/advanced care planning as well as their current status and needs. Some potential topics of discussion may be: preferred location of palliation, the cessation of certain medical interventions, comfort care options and preferences in the event of immanent death (e.g. resuscitation). The intent is to then have a written communication for the healthcare team to assist in the provision of individualized palliative care in a timely manner. Health status can change over time and this written plan should be reviewed in conjunction with shifts in status or changes in the care team. The goals of care can be amended or revised at any time by the individual and/or substitute decision* maker.

11.0 Palliative and End-of-Life Care

A palliative care approach should be applied when there has been a catastrophic stroke or a stroke in the setting of significant pre-existing comorbidity, to optimize care for these patients, their families, and informal caregivers [Evidence Level B].

i. The interdisciplinary stroke team should have discussions with the patient and decision-makers regarding the patient's current state and likely progression of the effects of the stroke, and come to agreement on the general direction of care - whether care will focus on comfort or focus on life prolongation and functional improvement [Evidence Level B].

ii. Based on decisions regarding the direction of care (i), the interdisciplinary stroke team should communicate with patients, decision-makers, families, and informal caregivers on an ongoing basis, and provide information and counseling regarding diagnosis, prognosis and what can be expected regarding progression of stroke impact, and management, based on direction of care (see recommendation i) [Evidence Level C].

iii. Content to be discussed with patients, families, and informal caregivers may include:

   a. the appropriateness of life-sustaining measures including mechanical ventilation, enteral/intravenous feeding, and intravenous fluids [Evidence Level B];

   b. reassessment of all medications, and recommendations for cessation of medications no

longer necessary when the goals of care shift to comfort measures only (e.g., antiplatelets, anticoagulants, statins, hypoglycemics) [Evidence Level C];

c. cessation of routine vital sign checks, bloodwork and diagnostic tests [Evidence Level C];

d. oral care [Evidence Level C];

e. assessment and management of pain [Evidence Level B];

f. assessment and management of delirium [Evidence Level C];

g. assessment and management of respiratory distress and secretions [Evidence Level B];

h. assessment and management of incontinence, nausea, vomiting, constipation, and skin and wound care [Evidence Level C].

i. assessment and management of seizures [Evidence Level C];

j. assessment and management of anxiety and depression [Evidence Level C]. Refer to Canadian Stroke Best Practice Recommendations *Mood, Cognition and Fatigue Module* section 1 for additional information [Evidence Level C];

k. Preferred location of palliative care (e.g. Home, Hospice another supportive living environment) [Evidence Level C];

l. Preferred person to be notified upon time of death [Evidence Level C].

iv. The interdisciplinary stroke team should have the appropriate communication skills and knowledge to address the physical, spiritual, cultural, psychological, and social needs of patients, families and informal caregivers who are receiving end-of-life care. There should be regular communication with the patient, family and informal caregivers to ensure that these needs are being met [Evidence Level C].

v. Advance care planning discussions should be documented and reassessed regularly with the active care team and substitute decision-maker [Evidence Level C].

vi. Patients, families, informal caregivers, and the health care team should have access to palliative care specialists, particularly for consultation regarding patients with difficult-to-control symptoms, complex or conflicted end-of-life decision making, or complex psycho-social family issues [Evidence Level C].

vii. Formalized palliative care processes and a team experienced in providing end-of-life care for stroke patients (especially nursing staff) should be considered to introduce and monitor standards of care provided to patients at the end of life [Evidence Level B].

viii. Organ donation should be discussed with families and caregivers as appropriate [Evidence Level C].

ix. Supportive counselling, funeral supports and bereavement resources should also be provided to families and caregivers, post patient death [Evidence Level C].

Rationale

Implementing stroke best practices can contribute to reductions in morbidity and mortality; however, stroke remains the third leading cause of death in Canada. Mortality rates in patients with hemorrhagic stroke are significantly higher than ischemic stroke in the hyperacute and acute phases of care, and both groups require expertise and clear information. There is evidence describing the unmet needs in stroke patients who are at the end of life. Recognizing and addressing the needs of the person with a life-limiting stroke or who is close to death after a stroke can enhance the quality of the time left and the satisfaction of the patient, family, caregivers, and the health care team.

System Implications

1. Established referral process to specialist palliative care services, either within the same organization or through telehealth technology in rural and remote locations.
2. Established referral process to spiritual care services.
3. Communication training for physicians, nurses, and allied health professionals that addresses supporting patients with poor prognoses and their families.
4. Protocols for advance care planning to elicit patient and family goals for care preferences, and ensure these are documented and communicated to decision makers and health care team members.
5. Palliative care protocols that are integrated into ongoing care delivery.
6. Information on palliative care and linkages to local stroke support organizations and their services should be available for staff to share with patients and families.

Performance Measures

1. Percentage of stroke patients who had a referral to specialist palliative care services during inpatient care.
2. Percentage of dying patients who were placed on an end-of-life care protocol.
3. Percentage of stroke patients who die in the location specified in their palliative care plan.
4. Family and caregiver ratings on the palliative care experience following the death in hospital of a patient with stroke.

Measurement Notes

a. Documentation for palliative and end-of-life measures may appear in consult notes, nursing notes, or physician notes. Just the presence of an order for palliative consultation should not be accepted as adequate documentation.

b. Data quality may be an issue with some of these performance measures. Improved documentation should be promoted among health care professionals.

c. Patient and family experience surveys should be in place to monitor care quality with end-of life situations.

Implementation Resources and Knowledge Transfer Tools

Health Care Provider Information

- Palliative Care Education for All Care Providers: http://pallium.ca/
- Burton and Payne Palliative Care Pathway: http://www.biomedcentral.com/1472-684X/11/22
- •Bernacki RE, Block SD. Serious illness communications checklist. Virtual Mentor [Internet]. 2013;15(12):1045–9. Available from: https://www.researchgate.net/profile/Rachelle_Bernacki/publication/259316398_Serious_Illness_Communications_Checklist/links/54463d190cf2f14fb80f2c96/Serious-Illness-Communications-Checklist.pdf
- Registered Nurses Association of Ontario Guidelines for End-of-Life Care http://rnao.ca/sites/rnao-ca/files/End-of-Life_Care_During_the_Last_Days_and_Hours_0.pdf
- Canadian Virtual Hospice: http://www.virtualhospice.ca/en_US/Main+Site+Navigation/Home/Topics/Topics/Decisions/Adva

nce+Care+Planning+Across+Canada.aspx

Patient Information

- "Your Stroke Journey": http://www.strokebestpractices.ca/wp-content/uploads/2015/03/YOURSTROKEJOURNEY.FINAL_.ENGLISH..pdf
- End of life care (Palliative Care): http://www.heartandstroke.com/site/c.ikIQLcMWJtE/b.6305405/k.23A7/Heart_Disease__Endoflife_care_palliative_care.htm
- Canadian Hospice Palliative Care Association Advance Care Planning Resource Commons: http://www.chpca.net/resource-commons/advance-care-planning-resource-commons.aspx
- Canadian Virtual Hospice: http://www.virtualhospice.ca/en_US/Main+Site+Navigation/Home/Topics/Topics/Decisions/Advance+Care+Planning+Across+Canada.aspx
- Post-stroke Checklist: http://www.strokebestpractices.ca/wp-content/uploads/2014/06/HSF%20Post%20Stroke%20Checklist_WEB.pdf

Summary of the Evidence 2018

Palliative care is a comprehensive approach to end of life care that aims to control pain, provide comfort, improve quality of life, and effectively manage patients' and their families' psychosocial needs. It is an important component of stroke care given that a high proportion of patients will die during their initial hospitalization. The palliative care needs of 191 acute stroke patients were evaluated using the Sheffield Profile for Assessment and Referral to Care (SPARC), a screening tool developed to be used in advanced illness, regardless of diagnosis. SPARC included domains related to physical, psychological, religious and spiritual, independence and activity, family and social issues (Burton et al. 2011). Patient dependence, defined as a Barthel Index score of <15 and increasing age were found to be independent predictors of palliative care need.

Holloway et al. (2010) compared the reasons for palliative consults for patients following stroke to conditions including cancer, congestive heart failure, chronic obstructive pulmonary disease, and dementia. Of the total stroke admissions during the 3-year study period, 101 (6.5%) were referred for a palliative care consult. Patients with stroke had the lowest (worst) mean Palliative Performance Scale scores compared with all other conditions. Compared to patients with other conditions, stroke patients who received a palliative care consult were more often referred for end-of-life issues and more likely to die in hospital. Patients who had suffered a stroke were more likely to be unconscious during the assessment and more frequently lacked the capacity to make or participate in their own medical care decisions. When compared by stroke sub type, patients who had suffered an ischemic stroke were the least likely to be referred for palliative care (3.2%) while those with a subarachnoid hemorrhage were referred most often (15.0%). Eriksson et al. (2016) used data from 1,626 patients included in a national quality register for end-of-life care that had died of stroke in a hospital or nursing home, and compared care during the last week of life with 1,626 patients in the same register who died of cancer, matched for place of death, age and sex. The odds of experiencing dyspnea, anxiety and severe pain were significantly lower for patients with stroke; however, family members of stroke patients were less likely to be offered bereavement follow-up. Patients were also less likely to be informed about transition to end-of-life care.

Palliative care pathways have been developed to ensure that in the last days of their lives patients

receive the most appropriate care possible. However, there is an absence of high-quality evidence to suggest that they are effective. In a Cochrane Review, Chan et al. (2016) sought studies that examined the use of an end-of-life care pathway compared with usual care for the dying. A single cluster RCT was identified (n=16 hospital wards), comparing an Italian version of the Liverpool Care Pathway (LCP-I), a continuous quality improvement programme of end-of-life care vs. usual care. In this trial, 232 family members of 308 patients who died from cancer were interviewed. Outcomes were assessed during face-to-face interviews of family members 2–4 months after the patient's death. Only 34% of the participants were cared for in accordance with the care pathway as planned. The odds of adequate pain control and control of nausea or vomiting were not significantly higher in the LCP-I group.

Several studies have examined the characteristics of patients who are transferred to palliative care units. San Luis et al. (2013) included data retrieved from chart review of 236 patients admitted to hospital with a confirmed diagnosis of stroke. 97 patients were transitioned to palliative care. These patients were more likely to be older, have atrial fibrillation, have more severe dysphagia on the first swallowing evaluation, left MCA stroke, higher initial stroke severity, received tPA, and admitted on a weekday. Gott et al. (2013) reported that the diagnosis of stroke was a strong predictor of transfer to palliative care among a mixed diagnosis group of 514 patients with palliative care needs (OR=8.0, 95% CI 2.5-25.9, p=0.001).

Decisions to withhold or withdraw life-prolonging treatments after stroke affect a substantial proportion of patients who have experienced a severe stroke. Alonso et al. (2016) reviewed the charts of 117 patients with ischemic or hemorrhagic, who died during hospitalization, to identify those with do-not-resuscitate-orders (DNRO), and therapy goal modifications with transition to symptom control. Factors that contributed to the decision to limit life-sustaining therapies were sought. A DNRO was made in 101 (86.3%) patients, usually within 48 hours of admission. 40 patients were transferred to palliative care after a mean of 5 days. 38 patients were not able to communicate at the time of decision making. Following transfer, monitoring of vital parameters (95%) and diagnostic procedures (90%) were discontinued. Antibiotic therapy (86%), nutrition (98%) and oral medication (88%) were never ordered or withdrawn. Low-dose heparin was withdrawn in 23% cases. All patients were maintained on intravenous fluids until death. Disturbance of consciousness at presentation, dysphagia on day 1 and large supratentorial strokes were independent predictors of decisions to withdrawing/ withholding further treatment. Patients died an average of 2.6 days following therapy restrictions.

Reference List and Evidence Tables

Evidence Table 4 and References available on website at www.strokebestpractices.ca

APPENDIX ONE

Canadian Stroke Best Practice Recommendations

Acute Stroke Management Writing Group 2018:

NAME	PROFESSIONAL ROLE	LOCATION	DECLARED CONFLICTS OF INTEREST
Boulanger, Jean Martin	Co-chair, Neurology Chief, Charles-LeMoyne Hospital, Associate Professor of Neurology, Sherbrooke University	Quebec	Boehringer Ingelheim; Pfizer; Bayer; Sanofi Aventis; Merk
Butcher, Kenneth	Stroke Neurologist, Professor, Division of Neurology, University of Alberta	Alberta	Bayer Canada; Boeringer Ingelheim; BMS/Pfizer
Gubitz, Gord	Stroke Neurologist, *Director, Neurovascular Clinic, Queen Elizabeth II Health Sciences Center;* Assistant Professor of Medicine (Neurology), Dalhousie University	Nova Scotia	Bayer; Boeringer Ingelheim; BMS/Pfizer
Stotts, Grant	Stroke Neurologist, Director, Ottawa Stroke Program, Ottawa Hospital; Medical Director, Champlain Regional Stroke Network; University of Ottawa	Ontario	No conflicts to declare
O'Kelly, Cian J.	Associate Professor of Neurologic Surgery, Program Director, Division of Neurosurgery, Department of Surgery, University of Alberta	Alberta	Medtronic; Microvention
Boyle, Karl	Stroke Neurologist, Assistant Professor, Division of Neurology Department of Medicine, University of Toronto Director, Inpatient Stroke Service, Regional Stroke Centre, Sunnybrook Health Sciences Centre	Ontario	No conflicts to declare
Braun, Leah	Advanced Care Paramedic	Manitoba	No conflicts to declare
Goddard, Tom	Emergency Physician; Assistant Professor of Emergency Medicine, Dalhousie University; Chief of Emergency Medicine Annapolis Valley Health	Nova Scotia	No conflicts to declare
Heran, Manraj K.S.	Associate Professor Diagnostic & Therapeutic Neuroradiology Director, Diagnostic Neuroradiology Fellowship Program Vancouver General Hospital	British Columbia	No conflicts to declare

	University of British Columbia		
Kanya-Forstner, Nick	Family physician. Associate Professor, Northern Ontario School of Medicine, Stroke Team Member, Timmins & District Hospital	Ontario	No conflicts to declare
Lavoie, Pascale	Neurosurgeon, Assistant Professor, Department of Surgery, Laval University; Hôpital de l'Enfant-Jésus	Quebec	No conflicts to declare
McClelland, Marie	Stroke and ED Nurse, Kelowna General Hospital	British Columbia	No conflicts to declare
Pettersen, Jacqueline A.	Cognitive/Behavioural Neurologist; Associate Professor, Div of Neurology, Dept of Medicine University of British Columbia; Northern Medical Program University of Northern British Columbia	British Columbia	No conflicts to declare
Purvis, Heather	Stroke Survivor, spokesperson for HSF in MB, "external reviewer" for Stroke Best Practice.	Manitoba	No conflicts to declare
Shamy, Michel C. F.	Early Career Stroke Neurologist, Assistant Professor, Department of Medicine, University of Ottawa, Attending Neurologist, The Ottawa Hospital, Associate Scientist, The Ottawa Hospital Research Institute	Ontario	No conflicts to declare
Snieder, Elizabeth	Social Worker, Neurosurgery Program, The Ottawa Hospital	Ontario	No conflicts to declare
Tampieri, Donatella	Professor of Radiology, Neurology and Neurosurgery, McGill University; Director, Department of Neuroradiology, Montreal Neurological Institute.	Quebec	No conflicts to declare
van Adel, Brian	Stroke Neurologist, Assistant Professor, McMaster University, Division of Neurology, Neurosurgery, and Diagnostic Imaging	Ontario	No conflicts to declare
Verbeek, P. Richard	Emergency Physician, Sunnybrook Health Sciences Centre; Medical Director, Sunnybrook Centre for Prehospital Medicine; University of Toronto	Ontario	No conflicts to declare

Whelan, Ruth	Acute Care Nurse Lead, University Hospital, Saskatoon	Saskatchewan	No conflicts to declare

Additional Members of the Endovascular Thrombectomy Treatment Subgroup:

NAME	PROFESSIONAL ROLE	LOCATION	DECLARED CONFLICTS OF INTEREST
Stotts, Grant * Co-Chair	Director, Ottawa Stroke Program, Ottawa Hospital; Medical Director, Champlain Regional Stroke Network; University of Ottawa	Ontario	No conflicts to declare
Goyal, Mayank Co-Chair	Director of Research, Professor, Department of Diagnostic Imaging, University of Calgary; Neuroradiologist/ Neurointerventionalist, Calgary Stroke Program	Alberta	**Medtronic, Stryker** – funded research to Univ of Calgary; Speaker/Consultant**, Microvention** – consultant for making stroke devices**, GE Healthcare** – licensing agreement for systems of stroke diagnosis
Blacquiere, Dylan	Stroke Neurologist, Horizon Health	New Brunswick	**Bayer** – speaker's bureau industry involvement
Casaubon, Leanne K.	Stroke Neurologist, Toronto Western Hospital	Ontario	**Bayer** – Ad board participant, speaker; **Medtronic** – independent neurological assessor for clinical trial; **NoNO** – site PI for clinical trial; **Covidien Canada** – Ad board participant
Eustace, Marsha	Stroke Neurologist, Health Sciences Centre, St. John's	Newfoundland and Labrador	No conflicts to declare
Ferguson, Darren	Neurointerventionalist, Saint John Regional Health Centre	New Brunswick and Labrador	No conflicts to declare
Hegedus, Janka	Stroke Neurologist, Vancouver Island Health Authority	British Columbia	No conflicts to declare
Jacquin, Grégory	Stroke Neurologist, Hôpital Notre Dame CHUM, Montreal	Quebec	No conflicts to declare
Kamal, Noreen	Program Manager, QuICR – Quality Improvement & Clinical Research, Alberta Stroke Program; Adjunct Assistant	Alberta	No conflicts to declare

	Professor, Dept of Clinical Neurosciences, Cumming School of Medicine, University of Calgary		
Kelly, Michael	Neurosurgeon, Royal University Hospital, Saskatoon	Saskatchewan	**Medtronic Inc** - proctor, **Penumbra** - speaker
Linkewich, Elizabeth	Regional Director, North & East GTA Stroke Network; Director, Regional Stroke Centre, Sunnybrook Health Sciences Centre	Ontario	No conflicts to declare
Lum, Cheemun	Neurointerventionalist, Ottawa Hospital	Ontario	No conflicts to declare
Mann, Balraj	Systems Leader, Alberta Health Services	Alberta	No conflicts to declare
Milot, Genevieve	Neurosurgeon, CHUL - L'Infant Jesus Hôpital, Quebec City	Quebec	No conflicts to delcare
Newcommon, Nancy	Nurse Practitioner, Calgary Stroke Program	Alberta	No conflicts to declare
Poirier, Pierre	Executive Director, Paramedic Association of Canada	Ontario	No conflicts to declare
Simpkin, Wendy	Stroke Navigator, Halifax Infirmary	Nova Scotia	No conflicts to declare
Tivedi, Anuraug	Neurologist, Winnipeg Regional Health Authority	Manitoba	No conflicts to declare

ACUTE STROKE MANAGEMENT EXTERNAL REVIEWERS 2018:

EXTERNAL REVIEWER	PROFESSIONAL ROLE	LOCATION
Camden, Marie-Christine	Neurologue spécialisée en maladies vasculaires cérébrales, Centre Hospitalier Affilié, Universitaire de Québec, Hôpital de l'Enfant-Jésus	Quebec City, Quebec
Fawcett, Adrian	Neurologist, Trillium Health Partners, Mississauga, Ontario; Associate Neurologist, Hamilton General Hospital	Mississauga, Ontario
Gill, Neala	Program Manager, Cardiovascular Health Nova Scotia, Nova Scotia Health Authority	Halifax, Nova Scotia
Hussain, M. Shazam	Director, Cerebrovascular Center Associate Professor, CCLCM | Staff, Vascular Neurology and Endovascular Surgical Neuroradiology Cerebrovascular Center, Cleveland Clinic	Ohio, USA

Khatri, Pooja	Professor of Neurology, University of Cincinnati Director of Acute Stroke Research, UC Stroke Team	Ohio, USA
Krings, Timo	The David Braley and Nancy Gordon Chair in Interventional Neuroradiology, Chief of Diagnostic and Interventional Neuroradiology, Toronto Western Hospital & University Health Network; Chief of Medical Imaging, Toronto Western Hospital, Professor, Departments of Radiology and Surgery, University of Toronto	Toronto, Ontario
Mackey, Ariane	Professeur agrégé de médecine, Université Laval, Québec, Directrice du Centre de Recherche en Neurovasculaire, CHU de Québec/ Hôpital de l'Enfant-Jésus	Quebec City, Quebec
McNicoll –Whiteman, Rhonda	Regional Stroke Best Practice Clinical Nurse Specialist, Neurosciences and Regional Stroke Program, Hamilton Health Sciences Part Time Assistant Clinical Professor McMaster University	Hamilton, Ontario
Nguyen, Thanh	Director, Neuroendovascular Service, Associate Professor, Neurology, Neurosurgery and Radiology, Boston Medical Center Boston University School of Medicine	Boston, Massachusetts, USA
Nucera, Antonia	Stroke Neurologist, Director, Stroke Program, Sant' Andrea Hospital	Rome, Italy
Patocka, Catherine	Clinical Assistant Professor, Department of Emergency Medicine, Cumming School of Medicine, University of Calgary	Calgary Alberta
Rempel, Jeremy	Interventional and Diagnostic Neuroradiologist, Associate Clinical Professor of Radiology and Neurosurgery, Partner – Medical Imaging Consultants, University of Alberta	Edmonton, ALberta
Roy, Danielle	Interventional Neuroradiologist, CHUM, Professor of Radiology, University of Montreal, Associate Researcher	Montreal, Quebec
Sopher, Sean	Stroke Nurse Practitioner, Royal Alexandra Hospital	Edmonton, Alberta
Silvaggio, Joseph	Vascular and Endovascular Neurosurgery Assistant Professor, Section of Neurosurgery Residency Program Director, Section of Neurosurgery, College of Medicine, Faculty of Health Sciences, University of Manitoba	Manitoba

Schwartz, Neil E.	Clinical Professor, Vice-Chair (Education) Director, Young Stroke Program, Program Director, Neurology Residency Medical Director, Clinical Neurosciences (G1/H1) Stanford Stroke Center Department of Neurology & Neurological Sciences, Stanford Health Care, Stanford University School of Medicine	California, USA

APPENDIX TWO: PREHOSPITAL STROKE SCREENING TOOLS

Table 2A: Standardized Acute Pre-Hospital Stroke Screening Tools

Assessment Tool Author	Items/Scoring	Sample	Reference Standard	Results (validity & reliability)
Cincinnati Pre-Hospital Stroke Scale (CPSS) **Kothari et al. 1999**	3 items: presence/absence of facial palsy; unilateral arm weakness; and speech impairment. Items simplified versions from the NIHSS. Abnormality demonstrated on one or more items is indicative of suspected stroke	171 patients with suspected stroke recruited through ED and inpatient neurology units. Mean age was 57.8 years, 58% male. Stroke/TIA prevalence: 49 (28.7%) Patients were assessed by 24 prehospital care providers (17 paramedics and 7 EMTs) and 2 NIH certified physicians, resulting in 860 total assessments.	Final discharge diagnosis of stroke	**Validity** Physicians: Sensitivity 1 abnormality 66%, 95% CI 49-80% 2 abnormalities 26%, 95% CI 14-43% 3 abnormalities 11%, 95% CI 3-26% Physicians: Specificity 1 abnormality 87%, 95% CI 80-92% 2 abnormalities 95%, 95% CI 90-98% 3 abnormalities 99%, 95% CI 95-100% Prehospital care workers: Sensitivity 1 abnormality 59%, 95% CI 51-67% 2 abnormalities 27%, 95% CI 21-35% 3 abnormalities 13%, 95% CI 8-20% Prehospital care workers: Specificity 1 abnormality 88%, 95% CI 86-91% 2 abnormalities 96%, 95% CI 94-97% 3 abnormalities 98%, 95% CI 96-99% The validity of this scale has been evaluated further, by both the scale developers and independent researchers. **Reliability** ICC for total scores among all prehospital workers was 0.92, 95% CI 0.89-0.93 ICC for total scores between prehospital workers and physicians was 0.92, 95% CI 0.89-0.93
Face Arm Speech Test (FAST)	3 items derived from the CPSS: facial palsy, arm weakness, speech disturbance. Assessment of speech is not dependent on the	487 patients admitted by ambulance, primary care physicians and ED referrals with suspected	WHO criteria	**Validity** Sensitivity: Diagnostic sensitivity of FAST associated with paramedic use was estimated to be 79%. PPV (arrival by ambulance): 78%, 95% CI 72-84%

Assessment Tool Author	Items/Scoring	Sample	Reference Standard	Results (validity & reliability)
Harbinson et al 2003	repetition of a stock phrase, as per CPSS, but assessed during by EMS during normal conversation with the patient. Abnormality demonstrated on one or more items is indicative of suspected stroke	stroke. Mean age was 72 years, 52% were female Stroke/TIA prevalence: 356 (73.1%). FAST was completed by paramedics over a 6-month period		The validity of this scale has been evaluated further, by independent researchers. **Reliability** Not assessed in this publication, but has been subsequently evaluated.
Los Angeles Prehospital Stroke Screen (LAPSS) **Kidwell et al. 2000 (Prospective validation study)**	6 items: 4 screening/history items (age>45 years, no history of seizures, symptom duration <24 hours, ambulation status at baseline not bedridden or wheelchair bound), blood glucose (between 60 and 400) level, a clinical assessment (of 3 items to identify obvious asymmetry: facial palsy, grip, arm strength). If the patient has positive criteria, a blood glucose level within the specified range and unilateral weakness on the clinical exam items, they are a positive screen for stroke.	206 patients (of 1,298 total runs) with neurological symptoms, who were noncomatose, with nontraumatic cause, who had a LAPSS screen conducted. Mean age was 67 years, 52% were male. Stroke/TIA prevalence: 36 (17.5%) LAPSS was completed by 18 paramedics over a 7-month period.	Hospitalized patients with final diagnosis of stroke	**Validity** Sensitivity: 91%, 95% CI 76-98% Specificity: 97%, 95% CI 93-99%) PPV: 86%, 95% CI 70-95% NPV: 98%, 95% CI 95-99% Accuracy: 96%, 95% CI 92-98% + LR: 31, 95% CI 16-147 - LR: 0.09, 95% CI 0-0.21 This validity of this scale has been evaluated further, by both the scale developers and independent researchers. **Reliability** Not assessed
Ontario Prehospital Stroke Screen (OPSS) Chenkin et al. 2009	At least one of the following symptoms must be present: unilateral leg/arm weakness or drift; slurred speech or muteness; unilateral facial droop), and the patient can be transported to arrive at a stroke centre within 3.5 hours of symptom onset.	325 patients transported to a stroke centre, who had been screened as positive by paramedics using the OPSS. Patients were identified through a National Stroke Registry. Mean age was 73.7 years, 47.4% were male. Stroke prevalence: 187 (58%)	Final discharge diagnosis	**Validity** Since all patients included in the sample, were screened as positive, sensitivity and specificity could not be calculated. PPV for acute stroke (1,2, or 3 positive signs): 89.5%, 95% CI 85.7-92.7% No additional validation studies have been conducted on this scale. **Reliability** Not assessed

Assessment Tool Author	Items/Scoring	Sample	Reference Standard	Results (validity & reliability)
		An unknown number of EMS workers conducted OPSS over a one-year period		
Melbourne Ambulance Stroke Screen (MASS) **Bray et al. 2005**	Combination of items from CPSS and LAPSS. The presence of any physical assessment item + a response of "yes" to all history items indicates a positive screen	100 MASS assessments were conducted on patients with suspected stroke (total of 5,957 paramedic calls during the study period) Stroke/TIA prevalence: 73 (73%) 18 paramedics conducted MASS assessments over a one-year period	Final discharge diagnosis	**Validity** Sensitivity: 90%, 95% CI 81-96% Specificity: 74%, 95% CI 53-88% PPV: 90%, 95% CI 81-96% NPV: 745, 95% CI 53-88% +LR: 3.49, 95% CI 1.83-6.63 -LR: 0.13, 95% CI 0.06-0.27 Accuracy: 86% (Validity of LAPSS and CPSS was also assessed. CPSS had highest sensitivity at 95%, LAPSS had highest specificity at 85%) This validity of this scale has been evaluated further, by the scale developers. **Reliability** Not assessed
Medic Prehospital Assessment for Code Stroke (MedPACS) **Studneck et al. 2013**	The scale was developed by combining the strongest elements of CPSS and LAPSS and included: eligibility criteria-no prior history of seizure; onset of symptoms ≤25 hours, blood glucose 60-400 mg/mL and a physical exam (facial droop, arm/leg weakness; speech difficulty; and gaze preference) The presence of any physical assessment item + a response of "yes" to at least one eligibility criterion item indicates a positive screen	416 patients with suspected stroke, transported to one of 7 hospitals. Mean age was 66.8 years, 45.7% were male. Stroke prevalence: 186 (44.7%) EMS reports and stroke GWTG-S registries were reviewed over a 6-month period	Final discharge diagnosis	**Validity** Sensitivity: 74.2%, 95% CI 67.2-80.2% Specificity: 732.6%, 95% CI 26.7-39.1% PPV: 47.1%, 95% CI 41.3-53.0% NPV: 61.0, 95% CI 51.8-69.6% + LR: 1.10, 95% CI 0.973-1.24 - LR: 0.791, 95% CI 0.582-1.07 The validity of the CPSS was also assessed (SN: 79%, SP: 24%) No additional validation studies have been conducted on this scale. **Reliability** Not assessed
Recognition	7-items: 2 clinical history items	160 consecutive	Final diagnosis	**Validity** (Prospective validation study)

Assessment Tool Author	Items/Scoring	Sample	Reference Standard	Results (validity & reliability)
of Stroke in the Emergency Room Scale (ROSIER) **Nor et al. 2005**	(loss of consciousness, convulsive fits/syncope) and 5 neurological signs of stroke (facial palsy/weakness, arm weakness, leg weakness, speech disturbance and visual field defect). A -1 is awarded for each clinical history item present and a +1 for each neurological sign. Total scores range from -2 to +5. A score >0 is associated with possible stroke.	patients with suspected stroke presenting to the Emergency Department (ED) Stroke/TIA prevalence: 101 (63.1%) Assessments were conducted by ED physicians during a one-year period	made by stroke consultant after review of symptoms and imaging findings	Sensitivity: 93%, 95% CI 89-97% Specificity: 83%, 95% CI 77-89% PPV: 90%, 95% CI 85-98% NPV: 88%, 95% CI 83-93% (Validity of LAPSS, FAST and CPSS was also assessed. CPSS had highest sensitivity at 85%, LAPSS had highest specificity at 85%). The validity of this scale has been evaluated further by independent researchers. **Reliability** Not assessed

PPV: Positive Predictive Value; NPV: Negative Predictive Value; LR Likelihood Ratio

Table 2B: Additional Screening Tools: Glasgow Coma Scale

Assessment Tool	Number and description of Items	Time to Administer	Reliability/validity	Interpretation of Scores	Sensitivity and Specificity	Training Required
Glasgow Coma Scale (GCS) Teasdale & Jennett 1974[1]	15 items in 3 categories: motor response (6 items), verbal response (5 items), and eye opening (4 items). Points are awarded for the best response in each category. Categories are summed to provide a total score.	Approximately 1 minute.	**Interobserver reliability**: Scale authors reported low rates of disagreement, but noted variations in motor responses based on stimulus used [2]. Reported agreements ranged 0.48 (verbal) to 0.72 (eye opening)[3] and from 0.39 – 0.79.[4] Percentage agreements have been reported as 90% overall, and as ranging from 83.8% (eye opening, right) to 98.7% (best motor response – left).[5] In addition, similar rates of between observer agreement have been reported in groups of experienced nurses (98.6% - 100%), newly graduated nurses	GCS scores range from 3 – 15, where 3 represents total unresponsiveness and 15 represents alert and fully responsive. Scores may be divided into categories by severity: 13-15 = mild; 9-12=moderate and ≤8 represents severe injury. [21]	Not reported	Yes.

Assessment Tool	Number and description of Items	Time to Administer	Reliability/validity	Interpretation of Scores	Sensitivity and Specificity	Training Required
			(94.3%-96.2%) and student nurses (77.3% - 100%).[6] **Construct Validity**: In review of GCS, evidence supports association between extent of brain damage and depth of coma as assessed on GCS. GCS scores significantly associated with length of coma ($p<0.0001$). [7] **Predictive Validity**: GCS score is a significant predictor of death following stroke [8, 9] or traumatic brain injury (modified by age and mechanism of injury) [10], though eye-opening may be less strongly associated than either the motor or verbal score components[11]. GCS scores are also predictive of survival (AUC=0.89), though eye-opening may not add to predictive accuracy [12]. GCS scores have been demonstrated to be predictive of Glasgow Outcome scores at 6 months to 1 year post injury [7, 13-16], Disability Rating Scale scores at discharge [17] and at 6 months[18], FIM scores at discharge[17, 19] and employment status at one-year[20].			

Table 2C. Prehospital Stroke Severity Scales

Assessment Tool Author	Items/Scoring	Sample	Reference Standard	Results
Field Assessment Stroke Triage for Emergency Destination (FAST-ED) **Lima et al. 2016**	6-items, 5 based on NIHSS 1. Facial palsy (0-1) 2. Arm weakness (0-2) 3. Speech changes (0-2) 4. Eye deviation (0-2) 5. Denial/neglect (0-2) 6. Time (documentation for decision making) not scored Total possible score: 9	741 consecutive patients enrolled in the STOPStroke study, who were admitted to 2 university-based hospitals with unilateral, complete occlusion of the M1 and M2 segments of the MCA or basilar artery, with onset of symptoms within 24 hours. Prevalence of LVO: 240 (33%)	CTA	A cut-point of ≥4 on FAST-ED had best performance Sensitivity: 0.61 Specificity: 0.83 PPV: 0.72 NPV: 0.82 Accuracy: 0.79 AUC:0.813 Performance of FAST-ED was also compared with NIHSS, RACE and CPSS scale
FAST-VAN **Wasyliw et al. 2018**	FAST + VAN (see description below)	172 consecutive stroke patients recruited from a single centre.	CTA	80 patients were positive for LVO, 58 were negative, based on CTA. PPV was 58%
Vision, Aphasia, and Neglect (VAN) **Teleb et al. 2016**	Patients are asked to raise both arms up and hold them up for 10 s. If the patient demonstrates any level of drift, weakness or paralysis, the assessment continues. Otherwise, patient is VAN -ve and screen ends. **Items** Visual disturbances: field cut, double vision, new-onset blindness (present/absent) Aphasia: Expressive, receptive, mixed (present/absent) Neglect: Forced gaze, unable to feel both sides at same time or doesn't recognize arm, ignoring	62 acute stroke codes at a single facility Prevalence of LVO: 19 (30.6%)	CTA	Performance of VAN was also compared with NIHSS ≥6 For VAN +ve patients Sensitivity: 1.00 Specificity: 0.90 PPV: 0.74 NPV: 1.00 Accuracy: 0.92 NIHSS≥6 Sensitivity: 1.00 Specificity: 0.79 PPV: 0.58 NPV: 1.00 Accuracy: 0.84

Assessment Tool Author	Items/Scoring	Sample	Reference Standard	Results
	one side (present/absent) Scoring: None If weakness present + ≥1 positive finding =VAN +ve			
Prehospital Acute Stroke Severity Scale (PASS) **Hastrup et al. 2016**	3 NIHSS items: 1. Incorrect month and/or age? (Level of consciousness (NIHSS item >0) 1 point 2. Gaze palsy and/or deviation (NIHSS item gaze>0) 1 point 3. Arm weakness (NIHSS item arm weakness >0) 1 point Total possible score: 3	3,127 patients included in the Danish Stroke Registry (2010-2015) who were treated with t-PA. 2/3 of sample was used for scale development and 1/3 for validation Prevalence of LVO: 35%	CTA/MRA	A cut-point of ≥2 on the PASS had the best predictive value: Using the Derivation cohort Sensitivity 0.66, 95% CI 0.62-0.66 Specificity: 0.83, 95% CI 0.81-0.85 AUC: 0.74, 95% CI 0.72-0.76 OR=9.22, 95% CI 7.5-11.40 PPV/NPV: 0.68/0.81 +LR/-LR: 3.84/0.42 The values were similar when using the validation cohort
The Los Angeles Motor Scale (LAMS) **Nazliel et al. 2008**	3 items: 1. Facial droop (absent=0, present=1) 2. Arm drift (absent=0, drifts down=1, falls rapidly=2) 3. Grip strength (normal=0, weak=1, no grip=2) Total possible score 5	119 patients included in a clinical trials registry at a stroke centre from 1996-2003, and patients included in the Get with the Guidelines Registry in 2005. Patients were included if they were last known well within 12 hours of presentation to the ED and had a final diagnosis of ischemic stroke in the anterior circulation Prevalence of LVO: 74 (62%)	MRA/CTA, or catheter angiography	AUC: 0.854 A cut point of ≥4 had the best predictive value for detecting LVO Sensitivity: 81% Specificity: 89% Accuracy: 85% +LR: 7.36 -LR: 0.21
Cincinnati Prehospital Stroke Severity Scale (CPSSS)	3 NIHSS items: 1. Conjugate gaze deviation (≥1 on NIHSS item for gaze) 2 points 2. Incorrectly answers to at least	Derivation cohort-624 patients with mild to severe stroke from 2 NINDS t-PA trials. Validation cohort-650 patients from the IMS-III	CTA	**Severe stroke** AUC: 0.89 A cut point of ≥2 had the best predictive value for severe stroke Using the derivation cohort Sensitivity: 89%

Assessment Tool Author	Items/Scoring	Sample	Reference Standard	Results
Katz et al. 2015	1 of 2 LOC questions (NIHSS age or current month) and does not follow at least 1 of 2 commands (close eyes, open and close hand) ≥1 NIHSS items LOC 1b and 1c. 1 point 3. Cannot hold arm (left, right or both) up for 10 seconds (≥2 NIHSS motor arm). 1 point Total possible score 4	trial Prevalence of LVO: 34% (validation cohort)		Specificity: 73% + LR/-LR: 3.30/0.15 Using the validation cohort: Sensitivity: 92% Specificity: 51% + LR/-LR: 1.89/0.1
Pérez de la Ossa et al. 2014 **Rapid Arterial oCclusion Evaluation Scale (RACE)**	5 NIHSS items: 1. Facial palsy (absent=0, mild=1, mod/severe=2) 2. Arm motor function (normal/mild=0, moderate=1, severe=2) 3. Leg motor function (normal/mild=0, moderate=1, severe=2) 4. Head and gaze deviation (absent=0, present=1) 5. Aphasia (R hemiparesis: performs both tasks correctly=0, performs 1 task correctly=1, performs neither tasks=2); Agnosia (Left hemiparesis: patient recognizes arm/impairment=0, does not recognize arm *or* impairment=1, does not recognize arm *and* impairment=2) Total possible score 9	Derivation cohort-654 patients with acute stroke or stroke mimic for whom a stroke code had been activated by EMS or a community hospital. Validation cohort-357 patients transferred by EMS to a stroke centre Prevalence of LVO: 178 patients (27%) had a LVO in derivation cohort vs. 76 (21.3%) in the validation cohort.	Transcranial Doppler, CT or MRA	In the derivation cohort, there was a strong correlation between RACE and NIHSS (r=0.76, p<0.01) In the validation cohort, a cut point of ≥5 had the best predictive value for detecting LVO Sensitivity: 85% Specificity: 68% PPV: 42% NPV: 94% The AUC for the RACE scale was 0.82, 95% CI 0.77-0.87 for the detection of LVO
3-Item Stroke Scale (3ISS) **Singer et al. 2005**	3 items: Disturbance of consciousness (no= 0, mild =1, severe= 2) Gaze and head deviation (absent= 0,	180 patients presenting to a stroke unit in 2002 with symptoms of stroke within ≤6 hours (28 patients had ICH).	MRI/MRA/CT	A cut point of ≥4 had the best predictive value for detecting MCA occlusions Sensitivity: 67% Specificity: 92% PPV: 74%

Assessment Tool Author	Items/Scoring	Sample	Reference Standard	Results
	incomplete gaze/head deviation=1, forced gaze/head deviation= 2) Hemiparesis (absent=0, moderate=1, severe= 2) Total possible score 6	Prevalence of LVO: 27 (15%)		NPV: 89% Accuracy: 86% Inter-rater reliability: Intraclass correlation co-efficient was 0.947; K for individual items were 0.77, 0.77 and 0.84

PPV: Positive Predictive Value; NPV: Negative Predictive Value; LR Likelihood Ratio; AUC Area under curve

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Useful links:

1) Cincinnati Prehospital Stroke Scale (CPSS) http://www.strokecenter.org/wp-content/uploads/2011/08/cincinnati.pdf

2) Los Angeles Prehospital Stroke Scale (LAPSS) http://www.strokecenter.org/wp-content/uploads/2011/08/LAPSS.pdf

3) There is a more detailed review of the GCS available at www.abiebr.com. There is also a review of the GCS posted at www.strokengine.ca.

APPENDIX THREE:

Canadian Stroke Best Practices Screening and Assessment Tools for Acute Stroke Severity

Assessment Tool	Number and description of Items	Time to Administer	Reliability/validity	Interpretation of Scores	Training Required
Neurological Status/Stroke Severity					
Canadian Neurological Scale (CNS)(1)	Items assess mentation (level of consciousness, orientation and speech) and motor function (face, arm and leg). Motor function evaluations are separated into sections A1 (and A2. A1 is administered if the patient is able to understand and follow instructions (5 items). A2 is administered in the presence of comprehension deficits (3 items)(1, 2)	5-10 minutes(1, 2)	**Interobserver reliability***: k ranged from 0.535(facial weakness) to 1.000 and there was no significant difference in agreement between physician and nurse raters(1); agreement between assessments by 2 nurses, r=0.924 – at the item level κ ranged from 0.535 (level of consciousness) to 1.00 (motor response- face)(2) **Internal consistency:** $\alpha \geq 0.89$ (neurologist, neurology student and nurse raters)(1); $\alpha = 0.792$(2) **Concurrent validity:** CNS scale scores correlated with the Mathew scale, Orgogozo scale, Scandinavian Stroke Scale, and the National Institutes of Health Stroke Scale – correlations ranged from –0.85 to 0.92(3); and with MCA Neurological Score scores (r=0.977), NIHSS scores r=-0.948 and Guy's Prognostic Scores (0.397)(4) **Construct validity (known groups):** CNS scores were significantly different (p<0.001) for patients grouped as "alive at home", "alive in care" and "dead" at 3 months(4) **Predictive validity**: Significant associations have been reported between the results of acute assessment using the CNS and length of hospital stay(5), mortality(2, 5, 6), functional outcome or independence at 3 months post stroke(4, 7) and at 6 months post stroke(2, 8).	Motor items are rated in terms of severity. Ratings are weighted and summed to provide a total score out of 11.5.(2) Higher scores represent decreasing levels of stroke severity or improved neurological status.	Yes
National	15 items: impairment	Approximatel	**Test-retest:** ranging from 0.66 (emergency department	Total scale score = 0-	Yes(11, 23,

Institutes of Health Stroke Scale (NIHSS)(9)	in LOC, ability to respond to questions/ obey simple commands, papillary response, gaze deviation, hemianopsia, facial palsy, resistance to gravity (weaker limb), plantar reflexes, limb ataxia, sensory loss, visual neglect, dysarthria and aphasia. Each item is graded on an ordinal scale from 0-3 or 0-4 where 0=no impairment.	y 6-7 minutes(9)	nurse clinician) to 0.77 (neurologist)(9); ICC = 0.93 (3 month test interval-assessment of videotaped patient) (10) **Interobserver reliability****: For total overall scores, mean kappa values have ranged from 0.61 – 0.96(9, 11, 12) while reported ICC values range from 0.95-0.96(10, 13, 14). Single item reliability has varied substantially; the limb ataxia item has most often demonstrated poor interobserver reliability(11, 13, 15, 16). **Internal consistency**: Person separation reliability = 0.32 for total sample, 0.73 (left hemisphere stroke), 0.62 (right hemisphere stroke)(16); α = 0.85 and ω = 0.96(14) **Concurrent validity:** NIHSS scores associated with Mathew scale, Orgogozo scale, Scandinavian Stroke Scale, CNS (r ranging from –0.85 to 0.92)(3) (De Haan et al. 1993); also with MCA Neurological Score scores (r=-0.95), CNS scores (r=-0.948) and Guy's Prognostic Scores (r=-0.38)(4) **Construct validity**: NIHSS scores associated with stroke volume on CT(9, 17) as well as with assessments of function(3) and HRQOL(18) **Construct validity (known groups):** NIHSS scores were significantly different ($p<0.001$) for patients grouped as "alive at home", "alive in care" and "dead" at 3 months(4); baseline NIHSS scores correlated strongly with TOAST classification(19) **Predictive validity**: NIHSS scores have been demonstrated to be predictive of function/impairment status(9, 19-21) and of discharge destination or place or residence(9, 22)	42. Higher scores reflect greater severity. Stroke severity may be stratified as follows: >25 = very severe, 15 – 24 = severe, 5 – 14 = mild to moderately severe and 1 – 5 = mild	24)
Pediatric National Institutes of Health Stroke Scale (PedNIHSS)(25)	This is a variation of the adult form NIHSS designed for use in individuals aged 2 – 18. All items from the original version have been retained; however, age	Not reported.	**Interobserver reliability:***** For *prospective administration*, reported ICC = 0.99 (95% CI 0.97, 0.99) between study neurologists. Item level agreement ranged from $K_w = 0.40$ (sensory) to 1.00 (LOC-commands)(25); When used for *retrospective derivation* of PedNIHSS scores, ICC=0.95 and item level agreement ranged from $K_w = 0.47$ (visual) to 0.93 (motor left and right arm items). (26)	All scoring strategies were retained from the adult version(25)	Yes. The scale authors provide a guide for administration in children aged 2-18.

	appropriate adaptations have been applied to language items, pictures and commands.		**Internal consistency reliability**: α=0.99(25)		
Glasgow Coma Scale (GCS)(27, 28)	15 items in 3 categories: motor response (6 items), verbal response (5 items), and eye opening (4 items). Points are awarded for the best response in each category. Categories are summed to provide a total score.	Approximately 1 minute.	**Interobserver reliability**: Scale authors reported low rates of disagreement, but noted variations in motor responses based on stimulus used(28). Reported agreements ranged 0.48 (verbal) to 0.72 (eye opening)(29) and from 0.39 – 0.79.(30) Percentage agreements have been reported as 90% overall, and as ranging from 83.8% (eye opening, right) to 98.7% (best motor response – left).(31) In addition, similar rates of between observer agreement have been reported in groups of experienced nurses (98.6% - 100%), newly graduated nurses (94.3%-96.2%) and student nurses (77.3% - 100%).(32) **Construct validity**: In review of GCS, evidence supports association between extent of brain damage and depth of coma as assessed on GCS. GCS scores significantly associated with length of coma (p<0.0001). (33) **Predictive validity**: GCS score is a significant predictor of death following stroke (34, 35) or traumatic brain injury (modified by age and mechanism of injury) (36), though eye-opening may be less strongly associated than either the motor or verbal score components(37). GCS scores are also predictive of survival (AUC=0.89), though eye-opening may not add to predictive accuracy(38). GCS scores have been demonstrated to be predictive of Glasgow Outcome scores at 6 months to 1 year post injury (33, 39-42), Disability Rating Scale scores at discharge(43) and at 6 months(44), FIM scores at discharge(43, 45) and employment status at one-year(46).	GCS scores range from 3 – 15, where 3 represents total unresponsiveness and 15 represents alert and fully responsive. Scores may be divided into categories by severity: 13-15 = mild; 9-12=moderate and ≤8 represents severe injury.(47)	Yes.
Assessment of Function					
Modified Rankin Scale (mRS)(56)	A global outcomes rating scale in which individuals are	15 minutes (via structured	**Interobserver reliability:** In a systematic review, there was substantial variability demonstrated with reported weighted kappa agreements ranging from 0.25 to 0.95. The authors	mRS scores range from 0-5 such that '0' is indicative of no	No. However, training

	assigned a subjective grade or rank ranging from 0-5 based on level of independence with reference to pre-stroke activities rather than observation of task-based performance. Modifications to the original scale have included expansion of the scale to include a "0" rank(57) and several changes to item wording (e.g. replacing disability with handicap).(58)	interview)(59, 60)	note, however, that reliability was often low, particularly in studies with larger sample sizes(61); Overall reported agreement was ICC=0.675, between the experienced and inexperienced raters K_w=0.686, agreement between experienced and inexperienced raters using a decision making tool K_w=0.568, and agreement between inexperienced raters without a tool and inexperienced raters with a decision tool was K_w=0.736(62) **Test-retest reliability**: K_w=0.95(63); k_w=0.94 for rater 1 and k_w=0.99 for rater 2 with a mean re-test interval of 7 days(59); κ=0.72 (based on re-assessment of videotapes, 3 month interval)(64) **Concurrent validity :** MRS scores correlated with the Barthel Index (3, 65-67), Functional Independence Measure(67), the Frenchay Activities Index(68) and the physical function scale of the SF-36.(66) **Convergent/discriminant validity:** In a comparison between mRS scores and scores obtained via the Sickness Impact Profile, there were stronger associations reported between SIP subscale assessments of functional ability (IADL), mobility and living arrangements and mRS scores than there were between mRS scores and SIP subscales of cognitive alertness or social interaction.(3) **Predictive validity** : pre-stroke mRS scores were an important predictor of post-stroke outcome assessed on both the Barthel Index and mRS.(66)	symptoms, while a rank of 5 is indicative of the most severe disability (described as bedridden, incontinent, requiring constant nursing care).(57)	and/or the use of structured interview tools has been associated with improved reliability.(59, 69, 70)
Functional Independ-ence Measure (FIM) (71)	18 items to evaluate 6 areas of function (self-care, sphincter control, mobility, locomotion, communication and	Approx. 30 minutes to administer and score; however, it is recommende	**Interobserver reliability**: In a review and meta-analysis (n=11 studies), interobserver reliability ranged from 0.89 to 1.0. When converted to a common metric and pooled, median agreement was reported to be 0.95(73) **Test-retest reliability**: In a review and meta-analysis (n=11	Items are scored on a 7-pt. Likert scale according to the amount of assistance required in the performance of each	Yes.

	social cognition). These may be placed into 2 domains; 1) motor (13 items: motor-FIM) and cognitive (5 items: cognitive-FIM).	d that ratings be derived by multidisciplinary team consensus following a period of observation.(72)	studies), median test-retest reliability was reported to be 0.95(73) **Internal consistency reliability:** Reported values for α range from 0.88(74) to 0.95(75, 76); reported item-to-total correlations range from 0.53 to 0.87(76). **Construct validity**: The 2-factor structure (motor + cognitive) of the FIM has been confirmed on factor analysis(77, 78), although a possible 3-factor model has also been reported (self-care, cognition, elimination)(79) **Concurrent validity**: Strong associations have been demonstrated between motor-FIM scores and scores from the Barthel Index(67, 74), the mRS(67), the Disability Rating Scale (DRS)(80), the Action Research Arm Test (81), The Fugl-Meyer Assessment(81), the Wolf Motor Function Test (time and functional assessment scores)(81) as well as between the cognitive-FIM and the DRS(80) **Construct validity (known groups):** FIM scores discriminated between groups right vs left-sided involvement in individuals with stroke at admission ($p<0.005$) and discharge ($p< 0.05$)(75); at admission and discharge, FIM scores were significantly different for individuals with and without neglect ($p<0.001$ and $p<0.02$, respectively) and with or without aphasia ($p<0.01$; $p<0.09$)(82). **Predictive validity:** admission (rehab) FIM has been reported to be associated with discharge FIM scores (total FIM, motor-FIM, cognitive-FIM)(83), length of inpatient rehabilitation stay(83, 84), functional gain(82), discharge assessments of balance and mobility(84), discharge walking speed(85) as well as discharge destination(75, 86). FIM scores have been reported to predict burden of care in terms of minutes of help/day required(87); motor-FIM scores have been associated with amount of direct assistance required, cognitive-FIM scores with direct supervision required(88); FIM scores at one month post stroke have been reported to be associated with depression at 3 months post stroke(89).	one (1=total assistance, 7 = total independence). Item scores are summed to provide a total out of 126. Motor and cognitive subscale scores may be calculated separately an may yield more useful information specific to each domain(77)	

Alpha-FIM(90)	A shortened version of the Functional Independence Measure. 6 items: 4 motor (eating, grooming, bowel management and toilet transfers) and 2 cognition items (expression and memory). If the individual with stroke is able to ambulate ≥150 feet then walking and bed-to-chair transfers may be substituted for eating and grooming items in the evaluation(91)	Approx. 5 minutes(92)	**Interobserver reliability:** ICC=0.92(92) **Internal consistency reliability:** α=0.87, item-to-total correlations ranged from 0.27 (toilet transfer) to 0.75 (memory)(90); α=0.90(92) **Construct validity:** A single factor/component has been identified on factor analyses, accounting for the majority of the variance in functional status(90, 92) **Concurrent validity:** Alpha-FIM scores were significantly associated with total-FIM scores (r=0.75), and there was no significant difference reported between projected and actual FIM scores(90); correlated with Barthel Index scores (r=0.68)(92) **Predictive validity:** Alpha-FIM scores obtained in acute care were predictive of FIM scores on admission to and discharge from rehabilitation(90, 91), length of stay(90, 91), FIM gain(91) and discharge to the community(90).	Items on the Alpha-FIM are scored as per the original FIM scale. Scale scores range from 6 – 42. Alpha-FIM scores may be transformed to projected FIM scores using a [proprietary] algorithm ranging from 18-100.(90)	Yes.

***A number of studies have examined the reliability of retrospective calculation of CNS scores based on documentation provided in medical records. In general, these studies have demonstrated consistently high (excellent) levels of interobserver(93-95) and internal consistency(93) reliability. **As for the CNS, investigators have studiied the use of the NIHSS for performing retrospective, chart-based evaluations.(94, 96, 97) In general, the reported reliability of these assessments is lower than that associated with the CNS and should be based upon neurologist reports where possible (94, 98). ***The PedNIHSS appears to maintain a high level of reliability when used for retrospective derivation of an NIHSS score. In addition, there was no significant difference demonstrated between scores derived prospectively vs. retrospectively (p=0.49)(26)*

Useful Links:

1. Additional information regarding the CNS, NIHSS, mRS, and FIM is available at www.ebrsr.com and at www.strokengine.ca
2. There is a site for international users of the NIHSS scale – it may be found here: http://www.nihstrokescale.org/ It provides links to the scale in English, as well as lots of good training information – but it also provides links to the scale in quite a number of other languages as well.
3. NIHSS booklet in PDF form: https://stroke.nih.gov/documents/NIH_Stroke_Scale.pdf
4. And to an online calculator: http://www.mdcalc.com/nih-stroke-scale-score-nihss/

5. Hunt and Hess Scale: http://www.neurosurgic.com/index.php?option=com_content&view=article&id=439&Itemid=607 or http://radiopaedia.org/articles/hunt-and-hess-grading-system (this page also supplies links to the Fisher scale and to the WFNS scale)
6. Fisher Scale: http://www.neurosurgic.com/index.php?option=com_content&view=article&id=438&Itemid=606
7. Here is a more descriptive presentation of the WFNS: http://www.strokecenter.org/wp-content/uploads/2011/08/WWF_scale.pdf
8. The Rankin scale has its own website: http://www.rankinscale.org/
9. The official site for the Alpha-FIM: http://www.udsmr.org/WebModules/Alpha/Alp_About.aspx

APPENDIX 4: SELECTION OF VALIDATED SWALLOW SCREENING AND ASSESSMENT TOOLS

Author/ Name of test	Components of test Details of validation study	Results of original validation study
Daniels et al. 1997 [1] "Any Two"	Items included: 6 clinical features-dysphonia, dysarthria, abnormal volitional cough (includes water-swallowing test), abnormal gag reflex, cough after swallow and voice change after swallow were assessed. Scoring: Presence of any 2 of the items distinguished patients with/without dysphagia Sample: 59 acute stroke survivors were studied within 5 days of hospital admission.	Diagnostic standard: VMBS exam Prevalence of dysphagia: 74.6% The sensitivities and specificities of individual items ranged from 31%-76.9% and 61%-88%, respectively. Overall: Sensitivity: 92% Specificity: 67%
Trapl et al. 2007 [4] The Gugging Swallowing Screen (GUSS)	Preliminary Assessment (vigilance, throat clearing, saliva swallow) Direct swallow (semisolid, liquid, solid swallow trials) Scoring: Total scores ranged from 0 (worst) - 20 (no dysphagia). A cut-off score of 14 was selected Sample: 50 first-ever acute stroke patients with suspected dysphagia	Diagnostic standard: fiberoptic endoscopic evaluation using the Penetration Aspiration Scale to interpret the results. Prevalence of dysphagia: 73% First group of 19 patients using the GUSS to identify subjects at risk of aspiration: Sensitivity: 100%, Specificity: 50% Second group of 30 patients Sensitivity: 100% Specificity: 69% Interrater reliability: Kappa=0.835
Martino et al. 2009 [5] The Toronto Bedside Swallowing Screening Test (TOR-BSST)	Items included: presence of dysphonia before/after water swallowing test, impaired pharyngeal sensation and abnormal tongue movement. Scoring: pass=4/4 items; fail ≥1/4 items Sample: 311 stroke patients (103 acute, 208 rehabilitation)	Diagnostic standard: VMBS exam. Prevalence of dysphagia: 39% Sensitivity: 96% Specificity: 64% Interrater reliability (based on observations from 50 subjects) ICC =0.92 (95% CI: 0.85-0.96)
Edmiaston et al. 2009 USA [6]	Items included: Glasgow Coma Scale score <13, presence of facial, tongue or palatal asymmetry/weakness. If no to all 3 items, then proceed to 3 oz water swallowing test. Scoring: If there is evidence of change in voice quality, cough or change in	Diagnostic standard: Mann Assessment of Swallowing Ability (MASA), performed by a SPL. Prevalence of dysphagia: 29%

Author/ Name of test	Components of test Details of validation study	Results of original validation study
Acute Stroke Dysphagia Screen	vocal quality 1 minute after water swallowing test = fail. Sample: 300 acute stroke patients screened by nurses within 8 to 32 hours following admission.	Sensitivity (Dysphagia): 91% Specificity: 74% Sensitivity (aspiration risk): 95% Specificity: 68% Interrater reliability: Kappa=94%
Turner-Lawrence et al. 2009 [7] Emergency Physician Dysphagia Screen	The two-tiered bedside tool was developed by SLPs. Tier 1 items included: voice quality, swallowing complaints, facial asymmetry, and aphasia. Tier 2 items included a water swallow test, with evaluation for swallowing difficulty, voice quality compromise, and pulse oximetry desaturation (≥ 2%). Patients failing tier 1 did not move forward to tier 2. Scoring: Patients who passed both tiers were considered to be low-risk. Sample: a convenience sample of 84 stroke patients (ischemic/hemorrhagic) screened by 45 ER MDs.	Diagnostic standard: formal assessment conducted by an SLP Prevalence of dysphagia: 57% Sensitivity: 96% Specificity: 56% Interrater reliability: Kappa=0.90
Antonios et al. 2010 [8] Modified Mann Assessment of Swallowing Ability (MMASA)	12 of the 24 MASA items were retained including: alertness, co-operation, respiration, expressive dysphasia, auditory comprehension, dysarthria, saliva, tongue movement, tongue strength, gag, volitional cough and palate movement. Scoring: Maximum score is 100 (no dysphagia). A cut-off score of 94 was used to identify patients at risk of dysphagia Sample: 150 consecutive patients with acute ischemic stroke were assessed by 2 neurologists shortly after admission to hospital.	Diagnostic standard: MASA conducted by SLP Prevalence of dysphagia: 36.2% Sensitivity: 87% & 93% Specificity: 86% & 84% Interrater reliability: Kappa=0.76
Schrock et al. 2011[9] MetroHealth Dysphagia Screen	5 Items included: Alert and able to sit upright for 10 minutes, weak, wet or abnormal voice, drooling, slurred speech and weak, or inaudible cough. Scoring: ≥1 items answered yes=failed screen Sample: 283 patients admitted to the Emergency department with acute stroke and screened for the presence of dysphagia by nurses	Diagnostic standard: VMBS Prevalence of dysphagia at 30 days: 32% Sensitivity: 95% Specificity: 55% Interrater reliability: Kappa=0.69

Appendix 1: Reference List for Table 1

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